ELECTROENCEPHALOGRAPHY
AND
CLINICAL NEUROPHYSIOLOGY
AN INTERNATIONAL JOURNAL

Vol. 9, Number 2 May 1957

THE EFFECT OF CHLORPROMAZINE AND METHOPROMAZINE ON THE ELECTRICAL ACTIVITY OF THE BRAIN IN THE CAT

P. B. BRADLEY, M.D. and A. J. HANCE, B.Sc.[1]

Department of Experimental Psychiatry, Medical School, Hospital Centre, Birmingham, England

(Received for publication: June 4th, 1956)

INTRODUCTION

The central depressant action of chlorpromazine, which has led to its extensive use in the management of chronically over-active psychotic patients (Delay and Deniker 1953; Elkes and Elkes 1954), has been investigated experimentally by a number of workers, many of whom have suggested a possible site of action for this drug. The induction of light sleep in patients receiving chlorpromazine led Terzian (1952) to suggest that the drug might be acting on the brain stem reticular formation, which has been shown by Moruzzi and Magoun (1949), and by Magoun (1952) and his co-workers to influence states of wakefulness in man and in animals. Das, Dasgupta and Werner (1954) injected chlorpromazine intravenously in monkeys and observed changes in the behaviour and EEG. They suggested that the changes which occurred could be explained by a depressant action on the reticular formation of the brain stem rather than an interference with sensory pathways. Other investigators have set out to determine the site of action more specifically. Hiebel, Bonvallet and Dell (1954) have shown that chlorpromazine reduces the cortical response to alerting stimuli (auditory and olfactory), and also to electrical stimulation of the arousal system and the intravenous injection of small quantities of adrenaline. They concluded that the drug depressed the spontaneous activity of the reticular formation and reduced its sensitivity to sensory stimuli. Longo, von Berger and Bovet (1954), working on curarised rabbits and the rabbit *encéphale isolé* preparation, obtained similar results and came to the same conclusion.

With the exception of the experiments by Das *et al.* (1954) on monkeys, all the investigations cited above were carried out on acute preparations in which only electrical responses could be studied. Das *et al.* studied changes in electrical activity of the brain simultaneously with behaviour when administering chlorpromazine, but these experiments were, of necessity, in restrained animals, and in three only were they able to record the EEG before the drug was given. The importance of studying the effect of drugs in conscious chronic preparations in which the electrical activity of the brain and behaviour

[1] Rockefeller Research Scholar.

can be observed simultaneously has been emphasised elsewhere (Bradley and Elkes 1956).

In this study, we have examined the effects of chlorpromazine and methopromazine on the behaviour and electrical activity of the brain in unrestrained conscious animals. We have also used these drugs in combination with other drugs whose effects are well known, and in a limited number of acute preparations.

METHODS

Adult cats, of both sexes, and weighing between 2.5 and 4.0 kg. were used in all experiments.

(*a*) *Conscious Chronic Preparations*

A total of 9 of these preparations has been used. The electrodes were implanted under aseptic conditions employing the technique which has been described previously (Bradley and Elkes 1953a). Experiments were carried out with the animal in a constant environment chamber in which behaviour could be observed through a slit in one wall, whilst the electrical activity was being recorded. This chamber, together with the recording apparatus, was placed in a sound-proofed room. At the beginning of each experiment the animal was allowed a period of acclimatization of 1-2 hours in the chamber before control recordings of electrical activity and an examination of behaviour were made. Observations of affect, sensory responses, motor activity and physiological state were entered on a suitably designed protocol. In this way behaviour observations were standardised for different observers and could be compared from one experiment to another.

In 3 of the chronic preparations a Collison cannula (Feldberg and Sherwood 1953) was implanted in addition to the electrodes, in order that drugs could be injected directly into the ventricles of the brain.

(*b*) *Acute Preparations*

These were the so-called *encéphale isolé* and *cerveau isolé* of Bremer (1935 and 1936) and, in a few experiments, barbitone anaesthetised preparations. The *encéphale isolé* was prepared by transecting the spinal cord at the C_1 level with a blunt leucotome under full ether anaesthesia, and the *cerveau isolé* by transection of the mid-brain at the intercollicular level. The latter operation was usually carried out by aspiration of brain tissue with a fine pipette, under direct vision through a hemicraniotomy. The opposite hemisphere was then used for electrical recordings. The femoral vein was cannulated routinely for the injection of drugs and either the femoral or carotid artery for the recording of blood pressure. This recording was made either on a kymograph using a mercury manometer, or on the same record as the electrical activity by means of an electronic manometer.

The electrodes used for recording the electrical activity of the brain in the acute preparations were identical with those implanted in the chronic preparations. The use of these did not involve exposure of the surface of the cortex and hence no special precautions as to control of temperature and dehydration were necessary. All recordings were made on Edison Swan portable four-channel recording equipment.

(*c*) *Drugs*

The drugs used were, as far as possible, prepared freshly for each experiment by dissolving the pure substance in sterile distilled water. In some cases manufacturers' solutions were used. The drugs employed were:

Chlorpromazine hydrochloride, 4560 R.P., Methopromazine acid maleate, 4632 R.P. (May & Baker, Ltd.); r-Amphetamine sulphate (Menley & James, Ltd.); d-Lysergic acid diethylamide (LSD 25) (Sandoz Products, Ltd.); Atropine sulphate, Physostigmine sulphate, Ephedrine hydrochloride (British Drug Houses, Ltd.); Neostigmine methylsulphate (Roche Products, Ltd.); 1-*nor*-Adrenaline bitartrate (Bayer Products, Ltd.).

RESULTS

(*a*) *In the conscious animal*

The electrical activity of the brain in the unrestrained conscious cat has been described previously (Bradley 1952; Bradley and Elkes 1956). This activity in the normal animal, correlates closely with the behavioural state. In the experiments described here, when the animals were left undisturbed they became drowsy and in some cases appeared to be asleep, often curled up in a characteristic

way. In this state, the electrical activity consisted of slow waves, often of large amplitude, together with bursts of spindles at 9-12 c/sec. (fig. 1 A). Suitable stimuli (auditory or tactile) caused an arousal or alerting response (Rheinberger and Jasper 1937), in which the cat lifted its head and opened its eyes, and in some cases rose to its feet. At the same time, the slow waves in the electrocorticogram were blocked and only low voltage fast activity at 15-30 c/sec. remained. This has been called the "alert" type of pattern and the slow waves and spindles have been called the "drowsy" pattern. If, after an arousal had been obtained, the animal was left undisturbed, it would usually return to the drowsy state and there was a corresponding change in the electrical activity. In some animals during this transition, bursts of rhythmic 5-8 c/sec. waves appeared in the electrocorticogram which have been associated with an intermediate, "quiet" behavioural state (fig. 1 B).

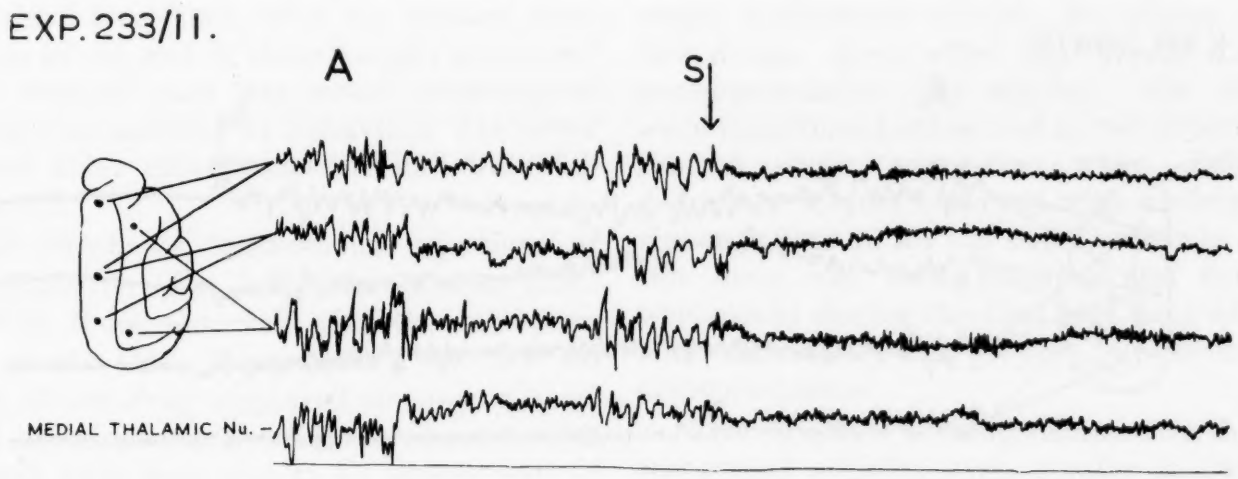


Fig. 1

Typical records of the electrocortical activity of a normal conscious cat in different behavioural states.

A. Arousal from the drowsy state through a sensory stimulus (noise) at "S".

B. Quiet.

(i) *Chlorpromazine*

This drug was used either alone or in combination with other drugs in a total of 68 experiments in conscious chronic preparations and in 36 of these experiments it was the first drug to be given. Consistent changes in the behaviour and in the electrical activity of the brain were observed with doses of 15 to

20 mg/kg. by intraperitoneal injection and 3.0 to 4.0 mg/kg. intravenously. The animals, which had been previously friendly or affectionate, became indifferent both to the environment and to the observer, and in 9 experiments were slightly aggressive when disturbed. Following chlorpromazine some ataxia was noted. The animals were unable to rise, stimuli (pinching the tail or paws) unless such stimuli were prolonged. Relaxation of the nictitating membrane was always observed, and in 13 experiments slight dilation of the pupils occurred. There was little change in the rate of respiration.

The electrical activity of the cortex reflected the changes in behaviour induced by

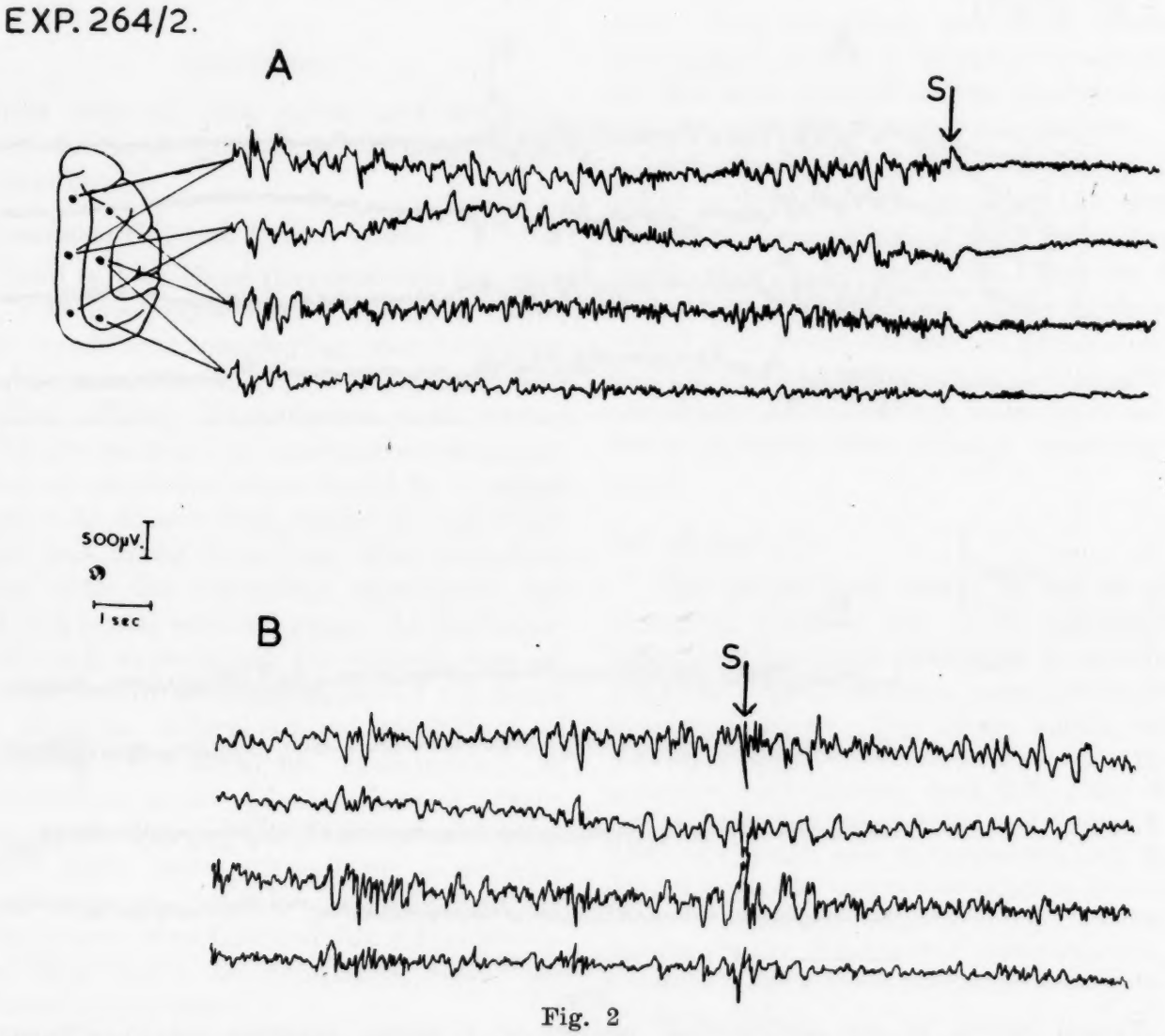


Fig. 2

Records from an experiment in a chronic preparation in which chlorpromazine was given by the intraperitoneal route.

A. Control record of the conscious animal showing arousal from the drowsy state through a sensory stimulus "S".

B. 20 min. after the injection of 15 mg/kg. chlorpromazine hydrochloride intraperitoneally. An arousal response could no longer be elicited at "S".

and if placed on their feet, they usually made no attempt to walk or remain standing, but sank to the floor immediately. Muscle tone remained unchanged, however. There was no longer any response to auditory, visual or tactile stimuli, and little response to painful the drug. The record was usually dominated by irregular waves at 5-8 c/sec. and with an amplitude of 150-250 μV. (fig. 2 B and 3 B). In one preparation this activity was seen to be more regular and at a slightly higher frequency (9-11 c/sec.) and in other animals,

lower voltage activity at 10-15 c/sec. accompanied the irregular 5-8 c/sec. waves. Slow waves at 2-4 c/sec., varying considerably in amplitude, were also observed. An arousal response could no longer be elicited after chlorpromazine had been given (fig. 2 B), and this was consistent with the absence of a behavioural response. In a few experiments the slow activity was slightly reduced in amplitude for 1 or 2 sec. after the arousal stimulus was given, and in these a slight movement of the head or ears was noted. Alerting of the electrical activity or behaviour was never observed after chlorpromazine had been administered.

The effects of intravenous injections of chlorpromazine (fig. 3 B) were almost identical with those observed with the intraperitoneal route, but the injection of 3.0 - 4.0 mg/kg. of the drug appeared to cause a brief loss of consciousness, lasting for about 1 min. This may have been due to an abrupt fall in blood pressure. There was also a temporary increase in the rate of respiration after intravenous injections.

Recovery from the effects of the drug was complete in 48-72 hours, and within 24 hours the animals were usually feeding normally.

In three preparations chlorpromazine was injected into the lateral ventricles of the brain through an implanted Collison cannula. In these experiments a sterile solution of pure chlorpromazine hydrochloride in distilled water was prepared each time. Following doses of 0.5 mg/kg. the animals were quieter and showed little interest in the environment, whilst the electrical activity consisted of rhythmic waves at 12-15 c/sec. with some slower components. With a total dose of 1.0 mg/kg., ataxia was more marked and there was no longer a response to sensory stimuli. The electrocorticogram showed 3-5 c/sec. irregular waves together with 12 c/sec. activity (fig. 3 C) and an arousal response could no longer be elicited. None of these effects was seen with control injections of distilled water.

(ii) *Methopromazine*

In 7 experiments in conscious chronic preparations methopromazine was injected intraperitoneally in doses of 20-30 mg/kg. The effects on behaviour closely resembled those observed with chlorpromazine; the animals became indifferent and ataxic, and showed no response to sensory stimuli. The nictitating membranes were relaxed, and in one experiment the pupils dilated. In none of these experiments was any change in the rate of respiration observed. However, there were minor differences between the effects of the two drugs. Even after the largest doses of methopromazine (30 mg/kg.) the animals were sometimes restless and in two experiments showed slight aggression when disturbed. A further feature observed with methopromazine was that in all the experiments in which this drug was used, retching and vomiting were noted during the first half hour after its administration; they were not seen with chlorpromazine.

The effects of methopromazine on the electrocortical activity were similar to those of chlorpromazine. In the above doses methopromazine caused irregular 4-7 c/sec. waves to appear together with smaller amplitude 11-14 c/sec. activity, and in most experiments there were some slow waves at 2-3 c/sec. as well. This pattern differed from that induced by chlorpromazine, in that it was interrupted for long periods by low voltage, fast activity, but this was consistent with the greater restlessness of the animals. In spite of the appearance of low voltage fast activity from time to time, the irregular activity, when present, did not respond to arousal stimuli.

(iii) *Combinations of chlorpromazine with amphetamine and lysergic acid diethylamide (LSD 25).*

R-amphetamine sulphate (2.0-5.0 mg/kg. intraperitoneally) and LSD 25 (15-20 μg/kg., intraperitoneally) both produce alerting of electrical activity and behaviour in the normal conscious cat (Bradley and Elkes 1953b, 1956), although their effects differ slightly according to the experimental conditions. In these experiments amphetamine caused the animals to become restless and in some cases excited, whilst the electrical activity was of the type seen in the fully alert animal, i.e. low voltage fast activity at 15-30 c/sec. (fig. 4B).

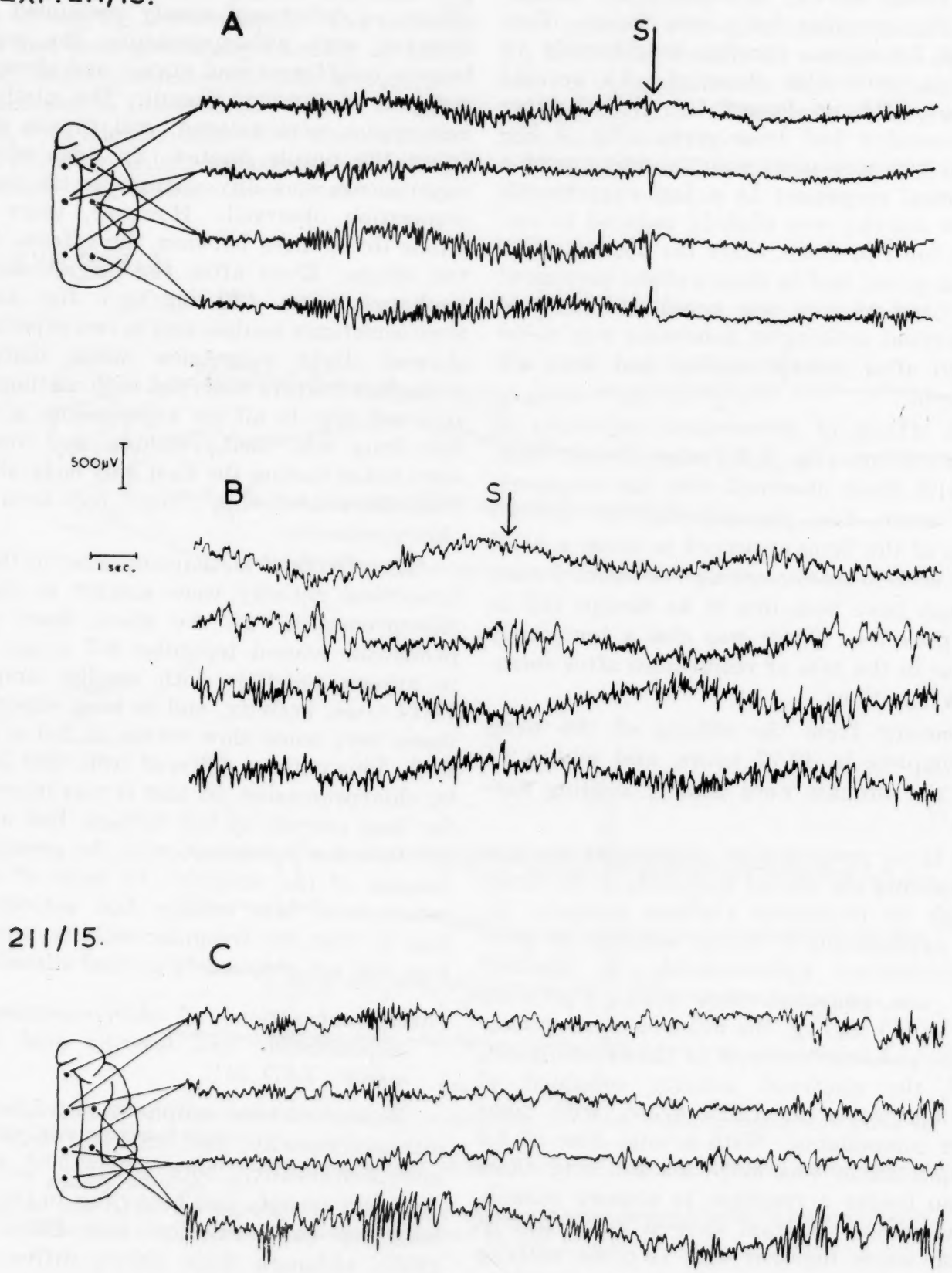


Fig. 3

Records from two separate experiments in the same preparation, in one of which chlorpromazine was given intravenously, and in the other into the lateral cerebral ventricle.

A. Control record showing an arousal response.

B. 16 min. after the injection of 4.0 mg/kg. chlorpromazine hydrochloride intravenously.

C. Another experiment with the same preparation, 16 min. after the injection of 0.6 mg/kg. chlorpromazine hydrochloride into the lateral ventricle of the brain.

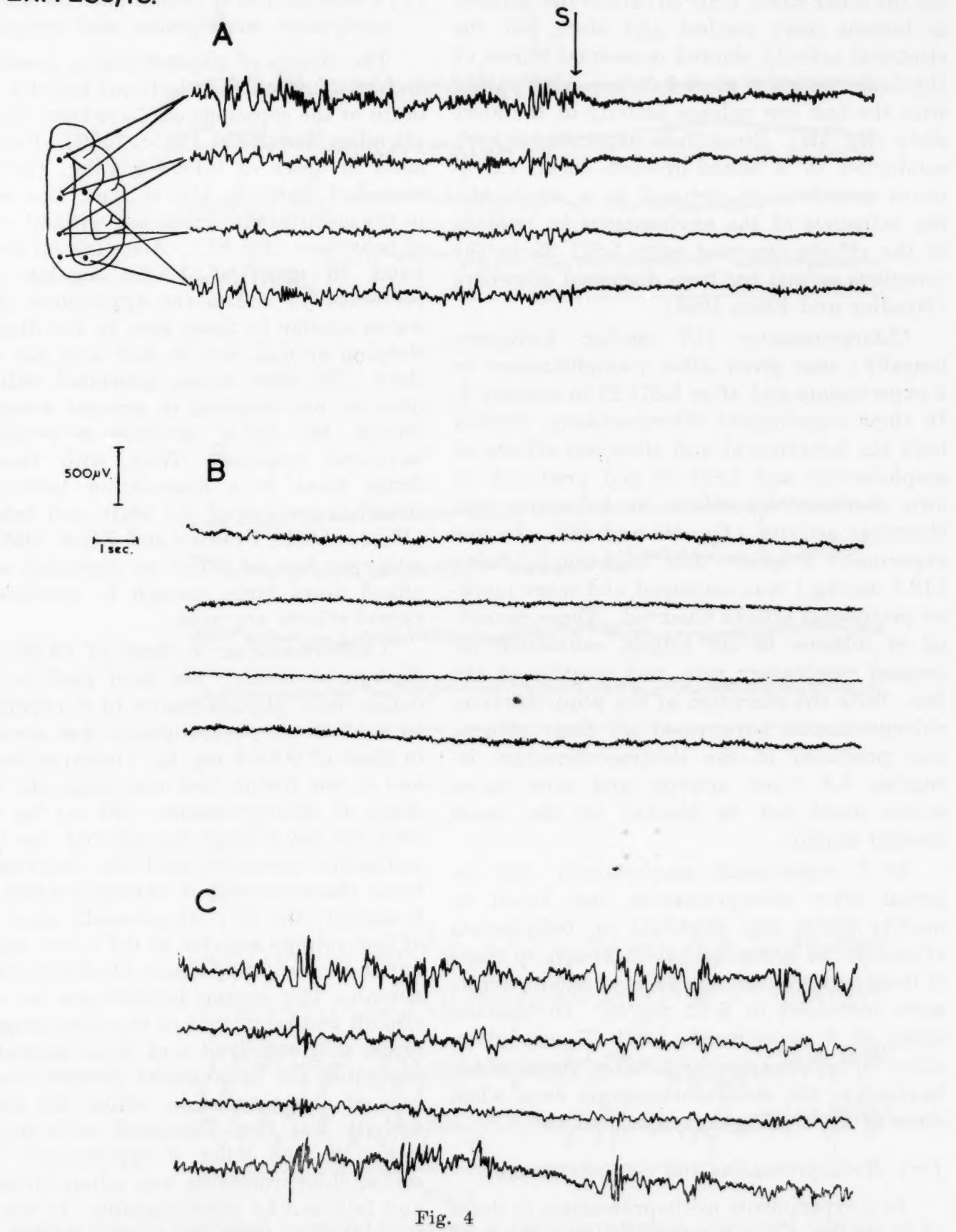


Fig. 4

Records from an experiment in which r-amphetamine was administered to the conscious cat and followed by chlorpromazine.

A. Control record showing arousal.

B. 15 min. after the intraperitoneal injection of 6.0 mg/kg. r-amphetamine sulphate.

C. 35 min. after the subsequent injection of 19 mg/kg. chlorpromazine hydrochloride intraperitoneally.

On the other hand, LSD 25 caused the animals to become more restless and alert, but the electrical activity showed occasional bursts of rhythmic activity at 4-6 c/sec. alternating with the fast low voltage activity of the alert state (fig. 5B). Since these experiments were conducted in a sound-proofed room, extraneous sounds were reduced to a minimum; the influence of the environment in relation to the effects observed with LSD 25 in the conscious animal has been discussed elsewhere (Bradley and Elkes 1956).

Chlorpromazine (15 mg/kg. intraperitoneally) was given after r-amphetamine in 4 experiments and after LSD 25 in another 4. In these experiments chlorpromazine blocked both the behavioural and electrical effects of amphetamine and LSD 25 and produced its own characteristic effects on behaviour and electrical activity (fig. 4C and 5C). In one experiment a larger dose of r-amphetamine (12.5 mg/kg.) was employed and more marked peripheral effects observed. These consisted of dilation of the pupils, salivation, increased respiratory rate, and erection of the fur. With the exception of the pupil dilation, chlorpromazine suppressed all these effects, and produced in the electrocorticogram irregular 5-8 c/sec. activity and slow waves which could not be blocked by the usual arousal stimuli.

In 7 experiments amphetamine was injected after chlorpromazine, but failed to modify either the electrical or behavioural effects of the latter drug even though, in three of these experiments, the doses of amphetamine were increased to 6-12 mg/kg. In another series of 5 experiments LSD 25 was given after chlorpromazine and failed to alter behaviour or the electrocorticogram even when doses of up to 90 μg/kg. were used.

(iv) *Methopromazine and r-amphetamine*

In 2 experiments methopromazine, in doses of 25 mg/kg. (intraperitoneally) was followed by amphetamine. The effects of the latter drug on electrical activity and behaviour failed to appear even when the dose was increased to 10 mg/kg. (intraperitoneally).

(v) *Combinations of chlorpromazine with physostigmine, neostigmine and atropine.*

The effects of physostigmine, neostigmine and atropine on the electrical activity of the brain of the conscious cat have been described (Bradley and Elkes 1953c, 1956). Physostigmine in doses of 0.1-0.4 mg/kg. (intraperitoneally) produces low voltage, fast activity in the electrocorticogram but without alerting of behaviour (fig. 6B). Atropine, on the other hand, in doses of 1.5-3.0 mg/kg. (intraperitoneally) causes the appearance of slow waves similar to those seen in the drowsy or sleeping animal, but in fact does not induce sleep. The slow waves associated with atropine do not respond to arousal stimuli, although the latter produce a normal behavioural response. Thus, with these two drugs there is a dissociation between the electrical activity of the brain and behaviour (Wikler 1952; Bradley and Elkes 1956). Neostigmine has no effect on electrical activity unless doses large enough to produce peripheral effects are used.

Chlorpromazine in doses of 13-30 mg/kg. (intraperitoneally) has been used in combination with physostigmine in 6 experiments. In 4 of these, physostigmine was given first in doses of 0.1-0.4 mg/kg. (intraperitoneally) and it was found that even when the largest doses of chlorpromazine (30 mg/kg.) were used, the low voltage fast activity due to physostigmine persisted, and the electrical patterns characteristic of chlorpromazine failed to appear (fig. 6C). Occasionally short bursts of low voltage activity at 6-7 c/sec. appeared but these were very easily blocked by sensory stimuli. The ataxia, indifference to sensory stimuli and relaxation of the nictitating membrane still appeared and these animals thus presented the behavioural picture characteristic of chlorpromazine, whilst the electrical activity was that associated with physostigmine. In the other 2 experiments in this series, chlorpromazine was administered first and followed by physostigmine. It was found that whereas the ataxia and indifference remained unchanged when physostigmine was injected, the slow and irregular 5-8 c/sec. electrical activity was abolished and replaced by low voltage fast activity (fig. 7c).

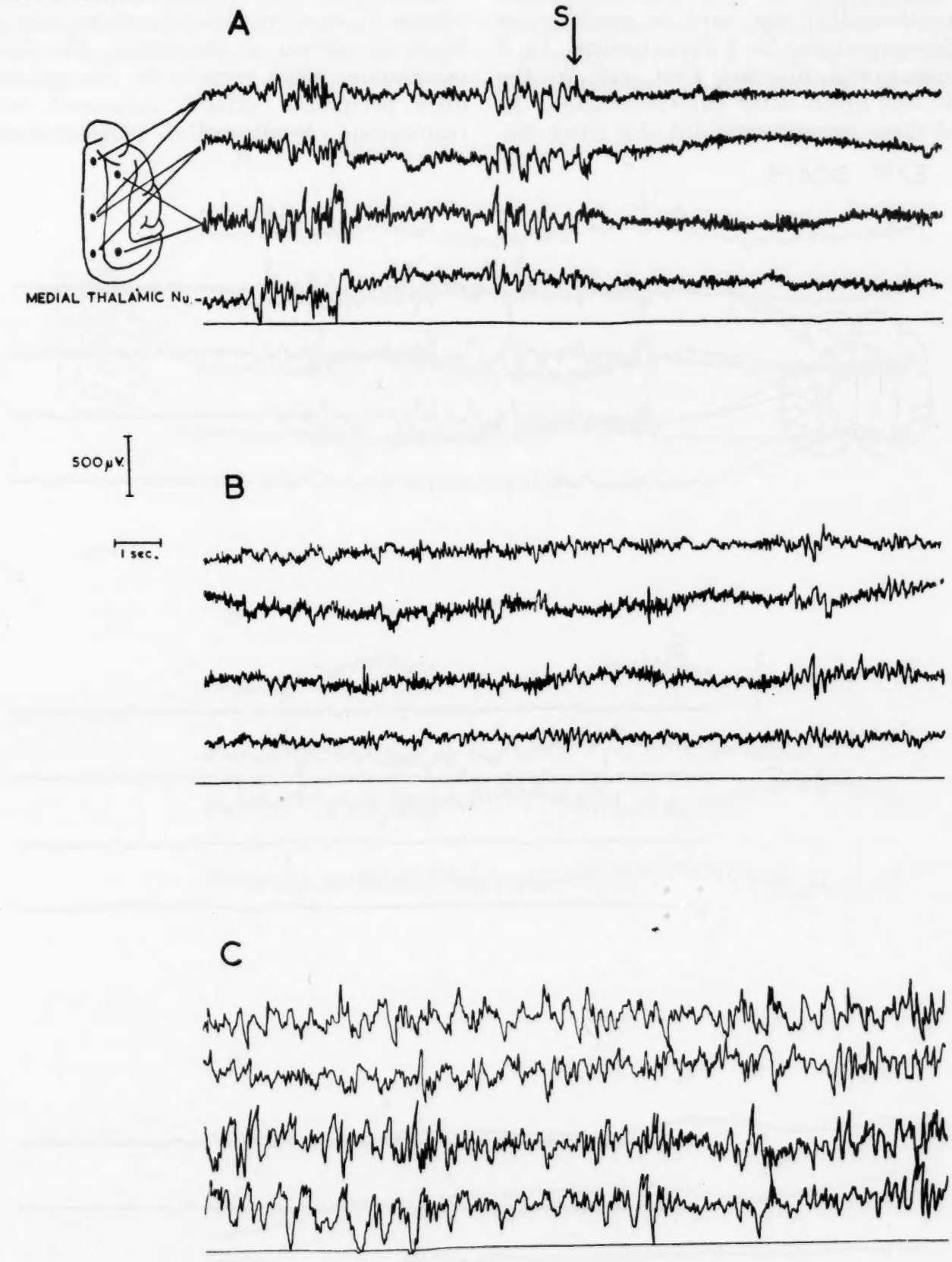


Fig. 5

Records from an experiment in which LSD 25 was given to the conscious animal and followed by chlorpromazine.

A. Control record showing an arousal response.

B. 12 min. after an intraperitoneal injection of 43 μg/kg. LSD 25.

C. 14 min. after the subsequent injection of 18 mg/kg. chlorpromazine hydrochloride intraperitoneally.

Neostigmine in doses of 0.1-0.4 mg/kg. (intraperitoneally) was used in combination with chlorpromazine in 3 experiments. In 2 neostigmine was injected first and in the other it was given after chlorpromazine. In none of these experiments did this drug modify in any way the behavioural and electrical effects induced by chlorpromazine, nor did it block the effects of the latter. The doses of neostigmine used were large enough to produce peripheral effects, increased rate of respiration, bradycardia, increased muscle

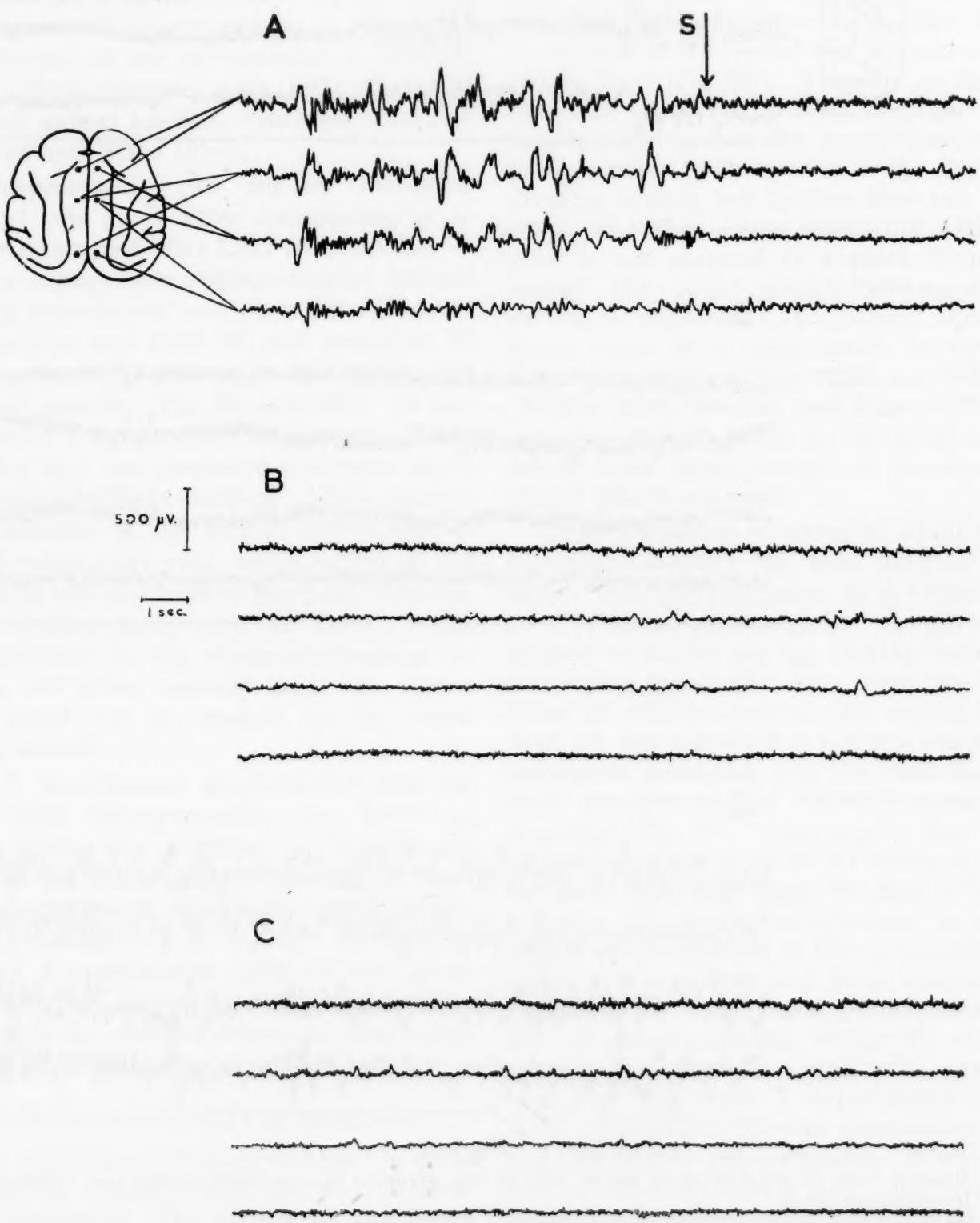


Figure 6

A. Control record of the normal conscious cat showing an arousal response.
B. 14 min. after an intraperitoneal injection of 0.1 mg/kg. physostigmine sulphate.
C. 21 min. after 15 mg/kg. chlorpromazine hydrochloride intraperitoneally.

tone, salivation, vomiting and defaecation. These effects, with the exception of salivation which was suppressed, were not blocked by chlorpromazine.

Atropine was used in combination with chlorpromazine in 12 experiments. The doses of atropine were 0.3-5.7 mg/kg., and those of chlorpromazine 7.4-32.0 mg/kg. In 7 exper-

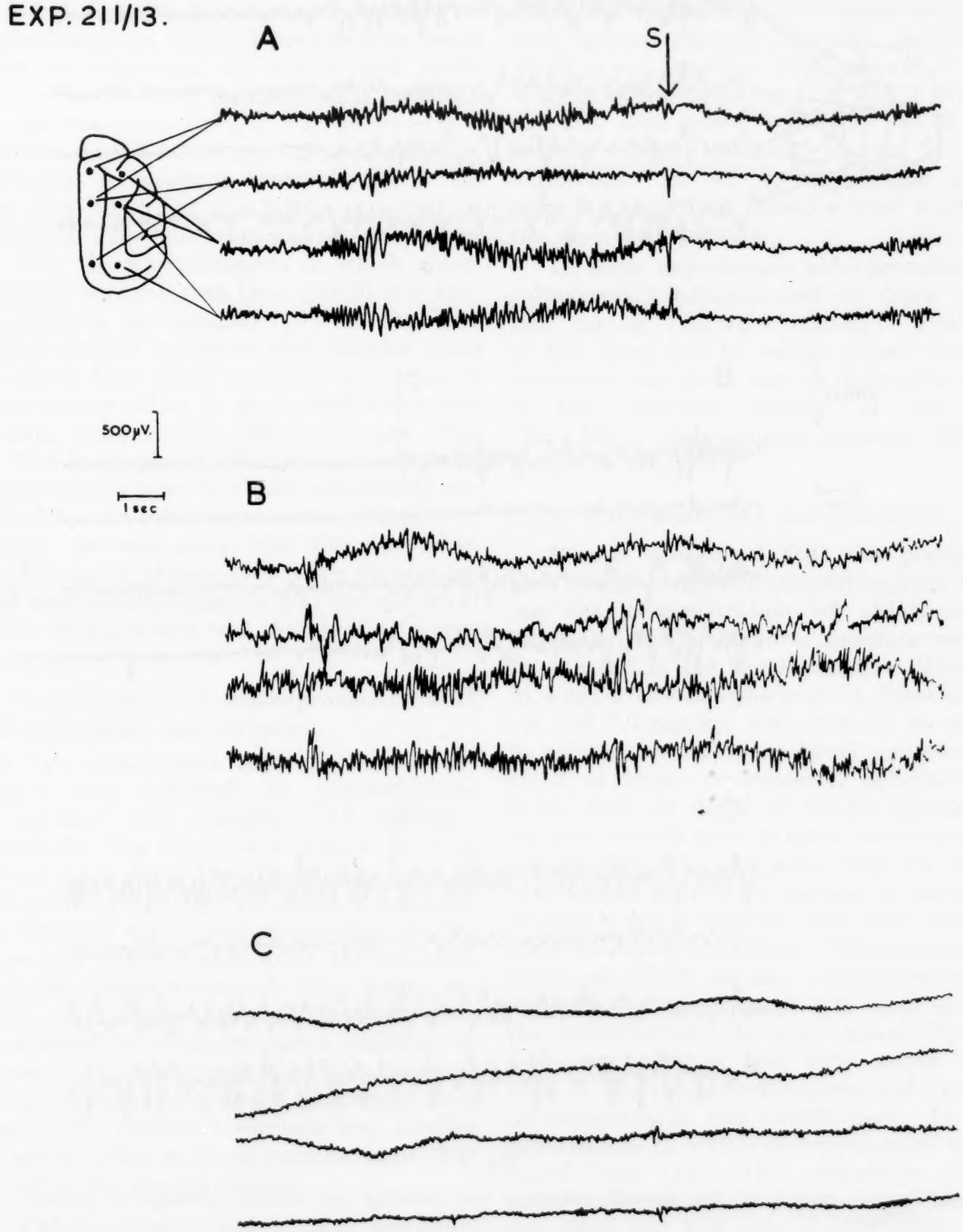


Fig. 7

A. Control record of the normal conscious cat showing an arousal response.
B. 17 min. after an intravenous injection of 4.0 mg/kg. chlorpromazine hydrochloride.
C. 25 min. after 0.2 mg/kg. physostigmine sulphate had been given intraperitoneally.

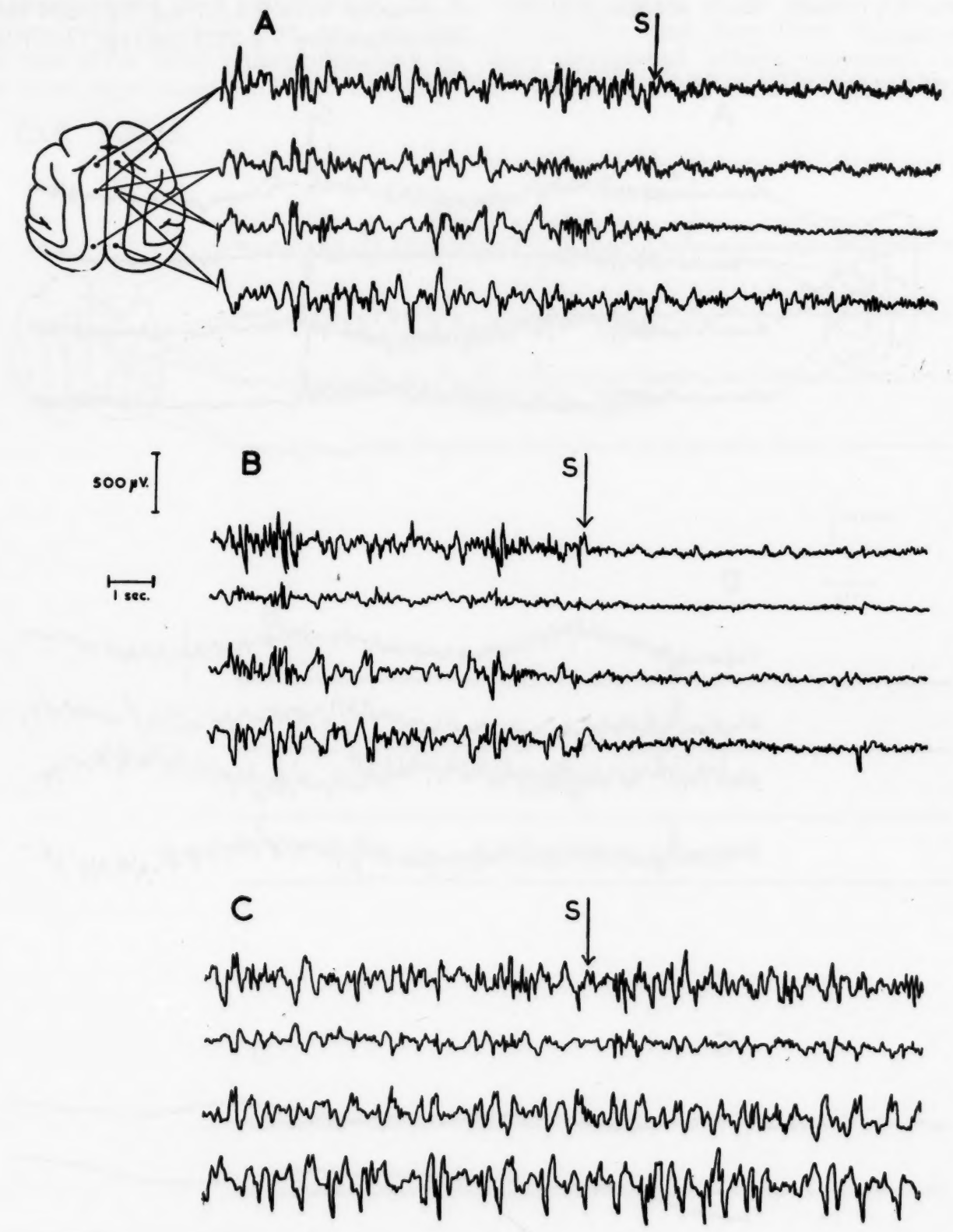


Fig. 8

A. Control record of the normal conscious cat showing an arousal through a sensory stimulus ''S''.

B. 47 min. after an intraperitoneal injection of 0.3 mg/kg. atropine sulphate, showing that a sensory stimulus ''S'' still produces an arousal response.

C. 45 min. after 15 mg/kg. chlorpromazine hydrochloride intraperitoneally. The sensory stimulus ''S'' no longer elicits an arousal response.

iments atropine was administered first, in 5 in doses sufficient to produce slow waves in the electrocorticogram which did not block with sensory stimuli (1.5-3.0 mg/kg.). When chlorpromazine was subsequently injected, it was found that this drug had no effect on the electrical activity, but still produced its usual effects on behaviour, i.e. ataxia and indifference. In the other 2 experiments in which atropine was given first, it was administered in smaller doses (0.3-0.6 mg/kg.). These were insufficient to produce continuous slow activity (fig. 8B), but the latter appeared in the record after chlorpromazine was given (fig. 8C). In 5 experiments in which chlorpromazine was injected first (15-20 mg/kg.) and followed by atropine (0.5-1.2 mg/kg.) the slow activity appeared with smaller doses of atropine than those required to produce a corresponding effect in an animal which had not been treated with chlorpromazine (fig. 9c). The behavioural effects associated with chlorpromazine were however, completely unaffected by the subsequent administration of atropine. As was seen with physostigmine, the behavioural effects here were those associated with chlorpromazine, but the electrical activity of the cortex was that typically seen with atropine.

(vi) *Combinations of methopromazine with physostigmine and atropine.*

In two experiments methopromazine (30 mg/kg.) was followed by physostigmine (0.2 mg/kg.) and atropine (0.5 mg/kg.), respectively. The effects were similar to those observed when these two drugs were used in combination with chlorpromazine. Physostigmine changed the electrical activity to low voltage fast activity and, after the injection of atropine, large amplitude slow waves appeared. In neither case was the behaviour state induced by methopromazine modified in any way. It was found that the dose of atropine required to produce continuous slow waves in the electrocorticogram was smaller when given after methopromazine than that required in the normal animal.

(vii) *Chlorpromazine and sodium pentobarbitone.*

Sodium pentobarbitone was used in 3 experiments with chronic preparations. In one it was given in a dose sufficient to produce mild sedation (7.0 mg/kg.), and in the other 2 to produce a light state of anaesthesia (11.5-18.0 mg/kg.). In the latter state the animals were not fully relaxed and still responded to painful stimuli, whilst the electrocorticogram showed spindle activity at 10-12 c/sec. together with some 6-10 c/sec. activity and slow waves (fig. 10B). With the smallest dose there was only 10-12 c/sec. activity which contained bursts at higher amplitude. In all 3 experiments sensory stimuli or handling caused a brief alerting of the electrical activity.

In these experiments chlorpromazine was subsequently administered in doses of 9.0-20.0 mg/kg. (intraperitoneally). The effect of this drug was to reduce muscle tone and movement but there was no detectable change in the electrical activity of the cortex (fig. 10C). An arousal response could no longer be elicited.

(viii) *Chlorpromazine and ephedrine.*

It was considered that the presence of slow waves in the electrocorticogram following the administration of chlorpromazine might be due to cerebral anaemia resulting from a fall in the blood pressure. Therefore, in 4 experiments, ephedrine in doses between 1.0 and 7.0 mg/kg. was given in an attempt to maintain or raise the blood pressure level. In 2 of these experiments, ephedrine was given first in doses of 2.0-3.0 mg/kg. and its main effects were to cause tachypnoea and pilo-erection. At the same time the electrocorticogram showed an increase in the amount of fast activity present, but this correlated with the behavioural state. Chlorpromazine in doses of 15-20 mg/kg. (intraperitoneally) reduced the respiratory rate and abolished the pilo-erection. It also caused irregular 5-8 c/sec. activity and slow waves to appear in the electrocorticogram and produced its usual ataxia and indifference. In the 2 experiments in which chlorpromazine was injected first (fig. 11B), ephedrine did not modify the behavioural affects produced by this drug and had only a very slight effect on the electrical activity. This consisted of a slight lowering of the amplitude of all frequencies recorded (fig. 11C).

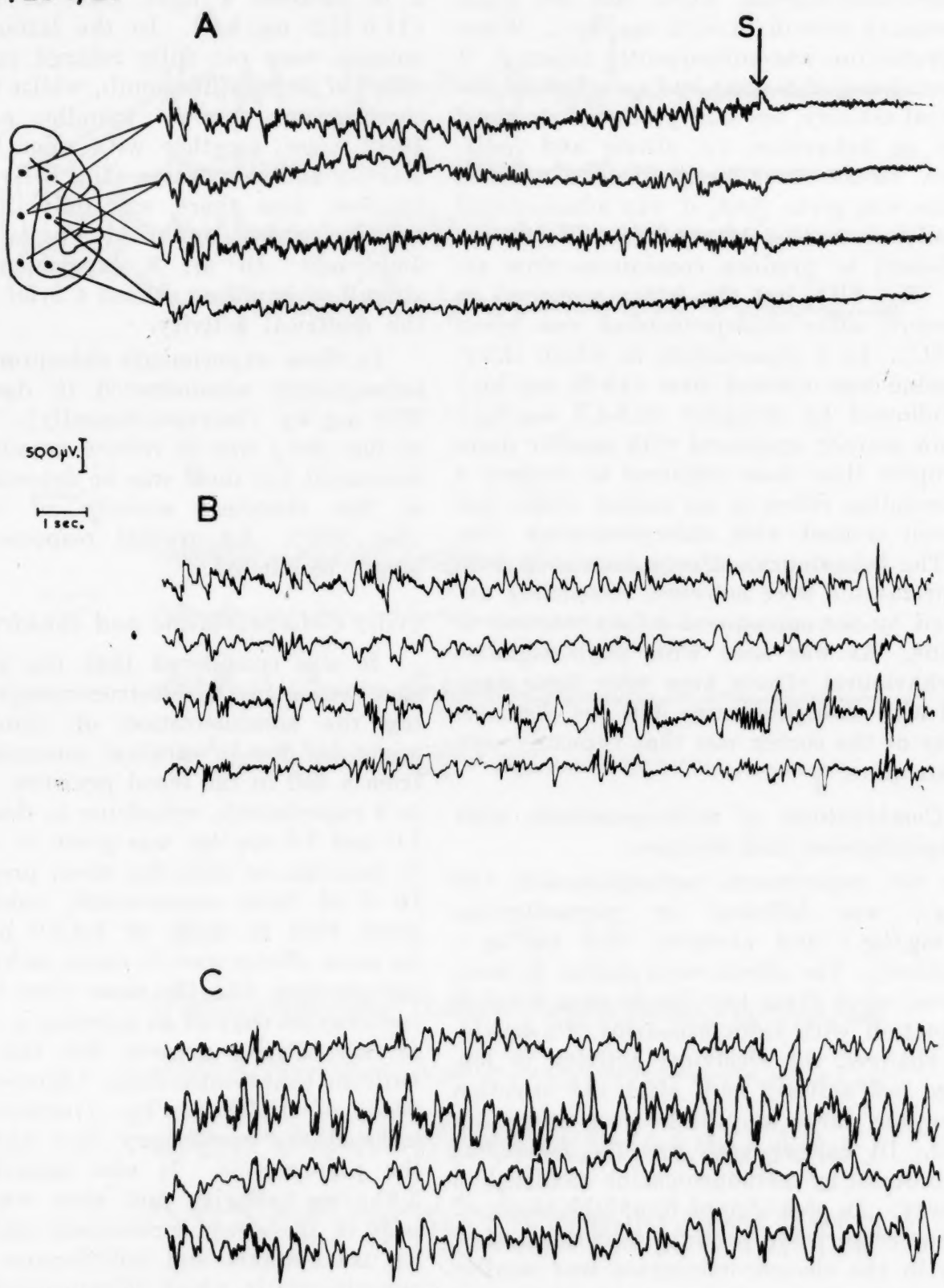


Fig. 9

A. Control record of the normal conscious cat showing an arousal response.
B. 35 min. after 15 mg/kg. chlorpromazine hydrochloride intraperitoneally.
C. 14 min. after the subsequent intraperitoneal injection of 1.2 mg/kg. atropine sulphate.

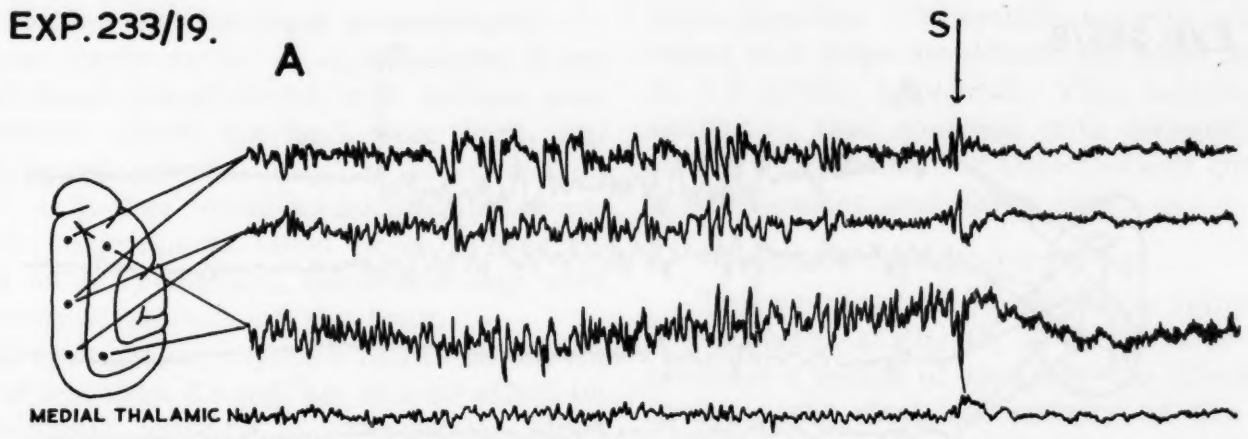


Fig. 10

A. Control record showing an arousal response in the normal conscious cat.
B. 40 min. after an intraperitoneal injection of 11.5 mg/kg. sodium pentobarbitone.
C. 50 min. after a subsequent injection of 21 mg/kg. chlorpromazine hydrochloride intraperitoneally.

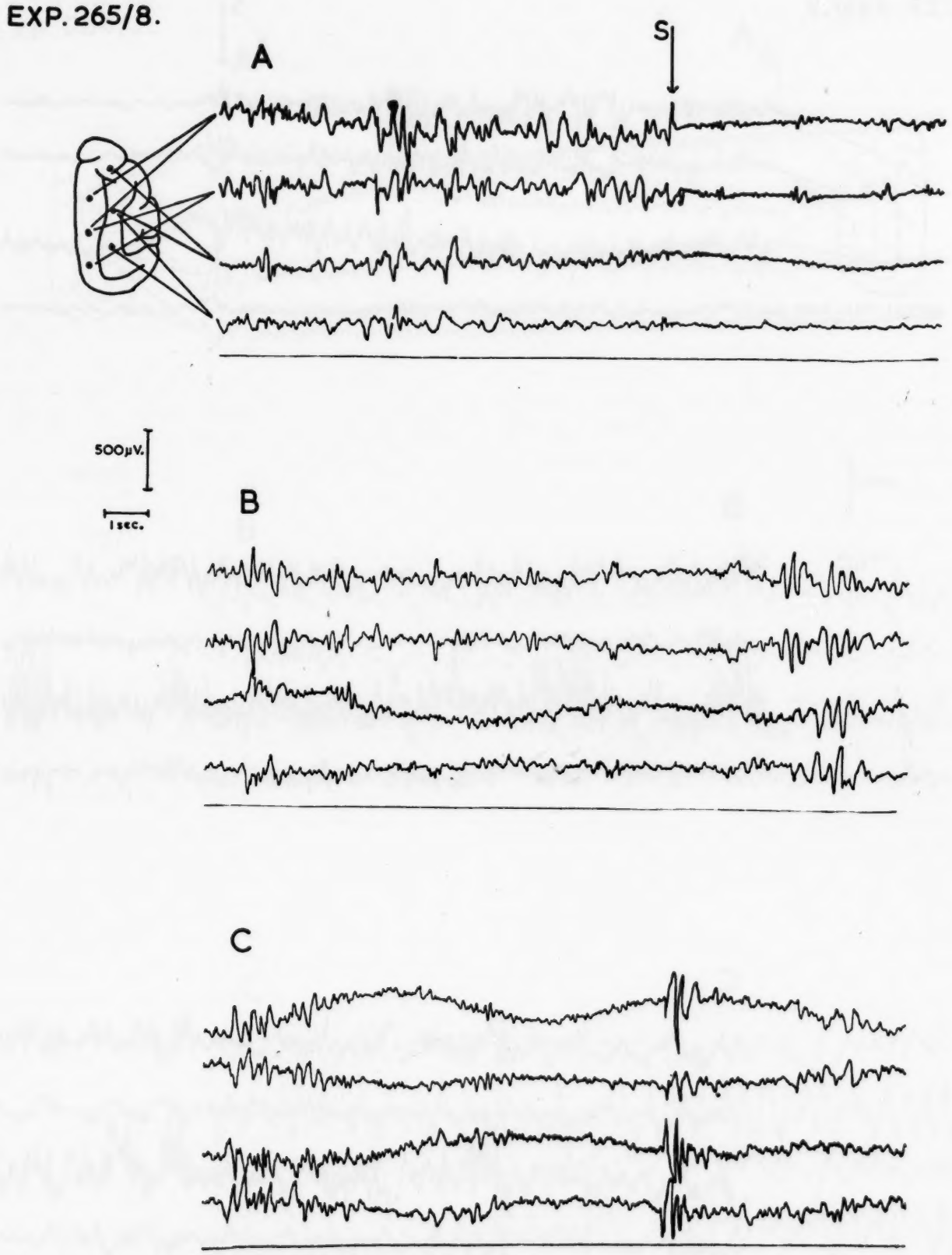


Fig. 11

A. Control record of the normal conscious cat showing arousal.
B. 60 min. after 15 mg/kg. chlorpromazine hydrochloride intraperitoneally.
C. 25 min. after an intraperitoneal injection of 2.0 mg/kg. ephedrine hydrochloride.

(b) *In acute preparations.*

1. *Barbitone anaesthetised preparations.*

In an early series of experiments, 5 cat preparations anaesthetised with sodium pentobarbitone (30-40 mg/kg.) were used, but this type of preparation was later discontinued, as it was found to be unsatisfactory. In these experiments blood pressure was recorded on a kymograph simultaneously with the electrical activity of the brain.

Chlorpromazine, injected intravenously in doses of less than 2.0 mg/kg. had no effect on the electrical activity of the cortex, blood pressure or cardiac rate. The immediate effect of doses greater than 4.0 mg/kg. was to cause a complete flattening of the electrical record corresponding to a sharp fall in the blood pressure of over 50 per cent. After an interval of 1 or 2 min. the blood pressure began to rise again slowly, and eventually slightly exceeded the previous mean before settling down to a constant level. The electrical activity reappeared as the blood pressure rose and consisted at first of rhythmic 6-10 c/sec. waves, followed by 5-7 c/sec. spindles. The only feature which distinguished the record following 4.0 mg/kg. or more of chlorpromazine from that of the animal under pentobarbitone alone, was that the frequency of the spindle activity was reduced from 8-10 c/sec. to 5-7 c/sec. Cardiac rate was unaffected unless doses of chlorpromazine in excess of 12 mg/kg. were used; these produced bradycardia. In 4 experiments *nor*-adrenaline was given as a continuous intravenous infusion, but did not prevent the blood pressure fall and disappearance of electrocortical activity following the intravenous injection of 4.0-13.0 mg/kg. of chlorpromazine.

In one experiment chlorpromazine was injected in divided doses into the lateral ventricle of the brain using a Collison cannula. Although a total dose of 0.6 mg/kg. was injected, no immediate changes in blood pressure or electrical activity were observed. Similarly, no effects were observed when chlorpromazine in doses of 1.5 and 3.5 mg/kg. was injected into the common carotid artery in one of the pentobarbitone anaesthetised preparations.

In one experiment in which 13 mg/kg. of chlorpromazine had been injected intravenously it was followed by 0.9 mg/kg. of physostigmine. The spindle activity was abolished and large amplitude rhythmic activity at 5-7 c/sec. appeared. This activity was similar to that observed with physostigmine alone in the barbitone anaesthetised preparations (Bradley and Elkes 1956).

2. *Encéphale isolé preparations.*

This preparation, in which the spinal cord is transected at the C_1 level (Bremer 1936) provides a means of studying the effects of a drug on the electrical activity of the brain and on blood pressure simultaneously. Since it still responds to arousal stimuli and two states, ''sleeping'' and ''waking'', can be distinguished both behaviourally and in terms of electrical activity, this preparation is particularly useful in the study of drugs which affect states of consciousness.

The effects of intravenous injections of chlorpromazine have been studied in eight *encéphale isolé* preparations and were of two types: (*a*) those which occurred in the first few minutes following the injection and were short lived, and (*b*) those which took longer to appear and which persisted throughout the experiment.

When comparatively small doses of chlorpromazine (0.2-1.0 mg/kg.) were injected intravenously, the spindles and slow waves characteristic of the sleeping state in the *encéphale isolé* preparation were either blocked or considerably reduced in amplitude (fig. 12B). The onset occurred between 30 sec. and 3 min. after the injection and the effect lasted for 30-120 sec. During this period the electrical activity consisted mainly of 10-15 c/sec. waves. The injection was usually accompanied by a slight transient rise and fall in blood pressure, but these changes were always complete before the blocking of the slow waves and spindle activity was observed. No changes in the behavioural state of the preparation were seen. Usually this effect was obtained only with the first injection; it was rarely seen with a second injection, even with small doses and it was never observed when doses greater than 1.0 mg/kg. were used.

Different effects were observed with doses in excess of 1.5 mg/kg. It was found that a

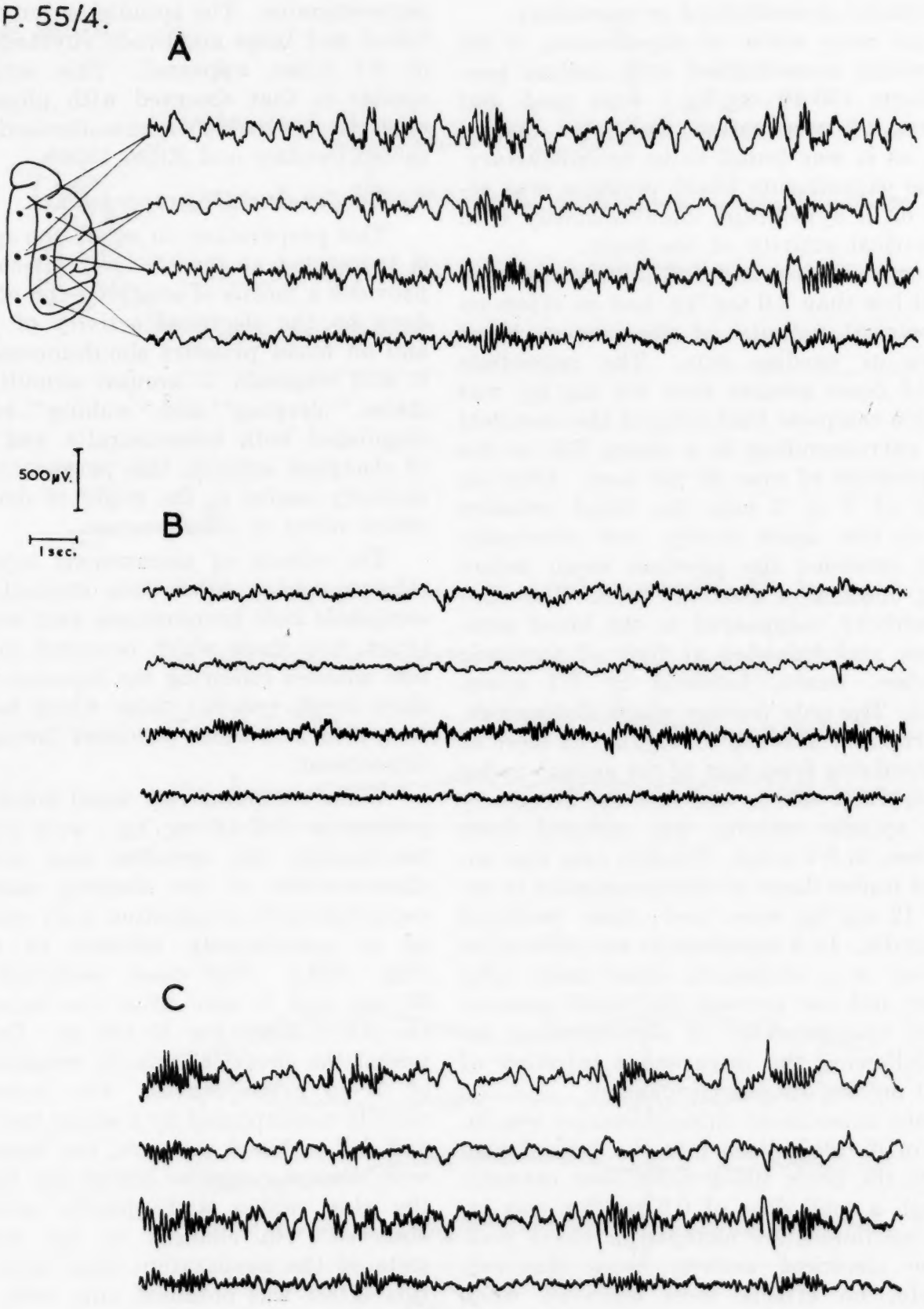


Fig. 12

Records from an acute experiment (*encéphale isolé* preparation) in which a small dose of chlorpromazine was given.

A. Control record with the preparation ''sleeping''.

B. 30 sec. after 0.5 mg/kg. chlorpromazine hydrochloride had been injected intravenously.

C. 2 min. after the same injection of 0.5 mg/kg. chlorpromazine hydrochloride.

preparation which had previously been easy to arouse by auditory or mild tactile stimuli (applied to the head), could no longer be alerted in this way and proved difficult to arouse even by handling. Slow waves at 1-3 c/sec. were increased in amplitude and were more continuous in the record, and irregular 5-8 c/sec. activity became more marked (fig. 13B). These effects persisted throughout the experiment. The injection of chlorpromazine in doses of 4.0-8.0 mg/kg. (intravenously) caused a fall in blood pressure and a corresponding flattening of the electrocorticogram, followed by a slow recovery similar to that seen with the barbitone anaesthetised preparation.

In two experiments in which *nor*-adrenaline was given as a continuous intravenous drip, it did not modify the effect of chlorpromazine although the mean arterial blood pressure was raised. The slow waves and irregular activity induced by the injection of 1.5-4.0 mg/kg. of chlorpromazine persisted in spite of the high blood pressure, and a further injection of 4.0-8.0 mg/kg. of chlorpromazine still caused a fall in pressure and flattening of the electrocorticogram.

In three experiments, ephedrine was injected intravenously in doses of 2.0-5.0 mg/kg. following chlorpromazine, but although a rise in blood pressure occurred, the electrical activity remained unaltered.

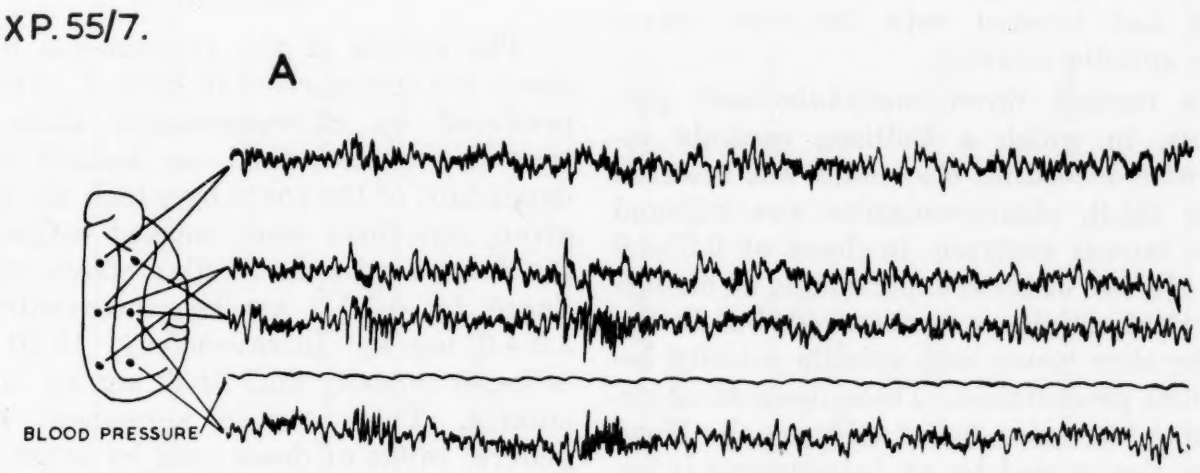


Fig. 13

Records from an acute experiment (*encéphale isolé* preparation).
A. Control record with the preparation "sleeping".
B. 4 min. after the intravenous injection of 2.0 mg/kg. chlorpromazine hydrochloride.

In one experiment in which 8.0 mg/kg. of chlorpromazine had been injected, it was followed by r-amphetamine in a dose of 16 mg/kg. The latter had no effect on the slow wave and spindle activity, although in the normal *encéphale isolé* it is effective in much smaller doses (1.5-3.0 mg/kg.). In this same preparation and in two others, 0.2 mg/kg. of physostigmine was subsequently injected and blocked both the slow waves and the spindle activity.

In a further three *encéphale isolé* preparations, in which a Collison cannula together with recording electrodes was inserted into the skull, chlorpromazine was injected into the lateral ventricle in doses of 0.25-4.0 mg/kg. In two of these experiments no change in electrical activity was observed, but in the third the slow waves and spindle activity became more pronounced. These doses of chlorpromazine were also found to block the blood pressure rise caused by an intravenous injection of 5-40 μg. of adrenaline.

3. *Cerveau isolé preparations.*

The effects of chlorpromazine were examined in 8 preparations of this type. In 4 the mesencephalic section was at the intercollicular level, passing rostrally to the sella turcica, and in the other 4 the section was slightly more caudal. In all except one, in which only a unilateral transection was made, the cortical activity consisted of slow waves or spindles and an arousal response could not be obtained. Chlorpromazine in doses of 0.2-2.0 mg/kg. had no effect on the electrocortical activity of these preparations and only the slight rise and fall in blood pressure associated with the injection was observed. In the preparation in which only a unilateral transection of the mid-brain had been performed, the effects following the injection of 0.5 mg/kg. of chlorpromazine were similar to those observed with small doses in the *encéphale isolé*, namely a transient blocking of the slow waves and spindle activity, lasting for about 60 sec. This preparation behaved in much the same way as an *encéphale isolé* preparation before chlorpromazine was injected, and it responded both behaviourally and electrically to arousal stimuli.

Doses of chlorpromazine in excess of 5.0 mg/kg. caused a pronounced fall in blood pressure and a flattening of the electrocortical activity similar to that observed when doses of this order were used with the *encéphale isolé* and barbitone anaesthetised preparations. In one experiment, however, this effect was observed with a dose of 0.2 mg/kg.

DISCUSSION

The results of the experiments described above are summarised in table I. The effects produced by chlorpromazine alone in the conscious unrestrained cat seemed to be independant of the route by which the drug was given, but there were marked differences in the doses required. Similar effects were produced by 0.5-1.0 mg/kg. intraventricularly, 3.0-4.0 mg/kg. intravenously, 15-20 mg/kg. intraperitoneally and 20-30 mg/kg. intramuscularly. These are in agreement with the general range of doses used by other workers. For example, Courvoisier *et al.* (1953) found that 10 mg/kg. was necessary to produce locomotor difficulty in dogs when given subcutaneously, and Boyd *et al.* (1953) used up to 40 mg/kg. orally. The intraperitoneal route, which was found to be the most convenient for repeated injections in the conscious cat, was used in most of our experiments, and accounts in some measure for the large doses employed. In all these experiments full recovery occurred within 48 to 72 hours and, despite repeated injections of chlorpromazine (and other drugs), the animals remained healthy and no change in their demeanour or behaviour was observed.

The effects which we observed with chlorpromazine in the conscious unrestrained cat are in close agreement with the findings of Das, Dasgupta and Werner (1954) in the conscious monkey. In all their experiments chlorpromazine was injected intravenously and they found that doses between 0.7 and 2.0 mg/kg. were required. We have had an opportunity to inject chlorpromazine intravenously into a number of monkeys and observe their behaviour. We found that in these animals, doses of 1.5 mg/kg. or less, frequently caused drowsiness. There would therefore appear to be a species difference

TABLE I

Drug	*Conscious Animal*		*Encéphale Isolé*	*Cerveau Isolé*	*Effects of Other Drugs After Chlorpromazine*	
	Behaviour	*Electrical Activity*	*Electrical Activity*	*Electrical Activity*	*Behaviour*	*Electrical Activity*
Chlorpromazine	Drowsiness and indifference	Slow and 5-8 c/sec. activity	Increased slow activity and spindles	No effect		
Physostigmine	Normal	Fast, low amplitude activity	Fast, low amplitude activity	Fast, low amplitude activity	No effect	Fast, low amplitude activity
Atropine	Normal or excited	High amplitude slow waves and spindles	High amplitude slow waves and spindles	High amplitude slow waves and spindles	No effect	High amplitude slow waves and spindles
Amphetamine	Excited	Fast, low amplitude activity	Fast, low amplitude activity	No effect	No effect	No effect
LSD 25	Excited	Fast, low amplitude activity	No effect	No effect	No effect	No effect

between the cat and monkey in terms of the effective intravenous dose of chlorpromazine.

It seems unlikely for a number of reasons that, with the exception of the immediate effects of the intravenous injections, the effect of chlorpromazine in the conscious animal was due to any depression of blood pressure by the drug. Firstly, in experiments on the anaesthetised dog, Courvoisier *et al.* (1953) found that intravenous injections of 1.0-5.0 mg/kg. had little effect on blood pressure, and our own experiments on barbitone anaesthetised preparations and on the *encéphale isolé* confirm this. When large enough doses to cause a blood pressure fall were used, the latter was usually transient, whereas the effects of chlorpromazine in the conscious animal persisted. Secondly, no change in blood pressure was observed by Cathala and Pocidalo (1952) when they injected 2.0 mg/kg. of the drug into the lateral ventricles although ataxia was produced. Our own experiments in which chlorpromazine was injected intraventricularly, both in the conscious animal and in the *encéphale isolé,* confirm this. Thirdly, the injection of ephedrine, either before or after chlorpromazine, did not block or modify the effects of this drug, although ephedrine still produced a rise in blood pressure when injected after chlorpromazine in the *encéphale isolé.* These facts lend support to the suggestion that the effects on behaviour and electrical activity of the brain observed with chlorpromazine in the conscious animal are due to a direct action by the drug on the central nervous system. This is further supported by the observation that intraventricular injections of chlorpromazine in the *encéphale isolé* blocked the pressor response to adrenaline.

Methopromazine produced effects similar to those which were observed with chlorpromazine, but the effects both on behaviour and on electrical activity were less marked in spite of the larger doses used. This compound, which differs from chlorpromazine only by the presence of a methoxy ($-OCH_3$) group instead of a chlorine atom on the phenothiazine nucleus (Charpentier *et al.* 1952), is reported to have similar pharmacological properties to chlorpromazine, although in some tests it was slightly less effective (May and Baker 1955). The difference between the effective doses of chlorpromazine and methopromazine in our experiments cannot be accounted for by the difference in the molecular weights of the salts in relation to the base (chlorpromazine being the hydrochloride and methopromazine the acid maleate). Thus, in terms of its central depressant effect, methopromazine would appear to be slightly weaker than chlorpromazine, as suggested by the difference in the doses required and by the qualitative differences in the effects.

In our experiments, chlorpromazine had no effect on the *cerveau isolé* preparation provided the midbrain transection was complete, and provided the doses used were insufficient to cause a marked drop in blood pressure. Das, Dasgupta and Werner (1955) have reported that small doses (0.2 mg/kg.) were sufficient to block the slow waves and spindles in this preparation. However, they do not say whether there was any corresponding change in blood pressure. In one of our experiments with this preparation we obtained a marked blood pressure fall with 0.2 mg/kg. and a corresponding blocking of cortical activity. In another preparation in which the midbrain transection was unilateral, the slow waves and spindles were temporarily blocked when chlorpromazine was injected. The effects obtained by Das, Dasgupta and Werner could therefore be due to either a change in the blood pressure level or an incomplete transection.

In our experiments, chlorpromazine had an effect on the intact animal and the *encéphale isolé,* but not on the *cerveau isolé* (table I). This suggests that the drug might be exerting its influence on some structure situated between the two planes of section of the acute preparations, i.e. between the upper spinal cord and the mesencephalon. This corresponds to the region in which the brain stem reticular activating system has been located (Magoun 1952) and is also the region which, for different reasons, has been suggested as the site of action of chlorpromazine by other workers (Terzian 1952; Hiebel *et al.* 1954; Longo *et al.* 1954). Further support for this suggestion comes from the results of the experiments in which chlorpromazine was used in combination with other drugs. The

effects of amphetamine and LSD 25, both on behaviour and electrical activity of the brain, were completely blocked by chlorpromazine. There is strong evidence to suggest that amphetamine, and possibly LSD 25 as well, produce their effects by an action on receptors situated at the level of the brain stem (Bradley and Elkes 1953b, 1956). The facts that neither chlorpromazine nor amphetamine have any effect on the *cerveau isolé* preparation and that chlorpromazine blocks the effects of amphetamine, both in the intact animal and in the *encéphale isolé,* support the suggestion that chlorpromazine exerts its depressant effect on the arousal system. The recent suggestion (Bonvallet, Dell and Hiebel 1954) that this system may contain an adrenergic element might form a possible link between the central depressant action and the anti-adrenaline action of chlorpromazine. The results of our experiments with intraventricular injections of this drug in the *encéphale isolé* indicate that the antagonism to the adrenaline pressor response may be a central effect.

When chlorpromazine was used in combination with atropine and physostigmine, it was noticed that these drugs still produced their characteristic effects on electrical activity, but the behavioural effects of chlorpromazine predominated. However, atropine and physostigmine produce effects on electrical activity in the conscious animal which are unrelated to behaviour and also influence the electrical activity of the *cerveau isolé* (Bradley and Elkes 1953c, 1956). This led us to suggest that it is unlikely that these drugs act on the brain stem reticular formation in producing the effects observed and that this system is probably not predominantly cholinergic. If chlorpromazine does act on the reticular formation and these drugs do not, then it might be expected that they would modify electrical activity whilst the behavioural effects of chlorpromazine persisted.

There seemed to be some synergism between the electrical effects of atropine and chlorpromazine since, when the latter drug was given, the doses of atropine required were from 5-10 times smaller than those needed for comparable effects in the untreated animal. This was independent of the order in which the drugs were given. It may possibly be related to the anti-acetylcholine properties of chlorpromazine which, though weak, have been measured peripherally (Kopera and Armitage 1954).

It is interesting to note that small quantities of chlorpromazine injected intravenously in the *encéphale isolé* preparation appeared to have a stimulating effect, since the sleep activity of this preparation was temporarily blocked. This effect was unrelated to changes in blood pressure and was not observed with larger doses, or with subsequent injections. It would appear that whilst the main action of chlorpromazine may be a central depression, in small doses it may have some excitatory effect. The depressant effect may take longer to appear, especially when smaller doses are used, and therefore the excitatory effect would be seen only with the first injection and with small doses.

The precise mechanism underlying the central depressant action of chlorpromazine is still a subject for speculation. It is known to have marked anti-adrenaline properties both peripherally (Courvoisier *et al.* 1953) and centrally (Hiebel *et al* 1954), and recently it has been shown to antagonise 5-hydroxytryptamine both *in vivo* and *in vitro* (Benditt and Rowley 1956). Both of these substances have recently been identified in the brain, and in higher concentrations in the hypothalamus and brain stem (Vogt 1954; Amin *et al* 1954). More recently Wase, Christensen and Polley (1956) have shown that chlorpromazine labelled with radioactive sulphur (S^{35}) accumulated in the hypothalamus. These observations, together with the results of the experiments described here, strongly support the hypothesis that chlorpromazine depresses the arousal system situated at the level of the brain stem, and it may do so by interfering with a system pharmacologically related to a centrally acting catechol amine.

SUMMARY

1. The effects of chlorpromazine and methopromazine on the electrical activity of the brain and on behaviour have been studied in the conscious unrestrained cat. Both produced ataxia and indifference together with slow and irregular 5-8 c/sec. waves in the electrocorticogram. These effects were less

marked with methopromazine. With chlorpromazine the effects seen were independent of the route used, but different doses were required.

2. Both drugs blocked the effects on behaviour and electrical activity which are normally observed with amphetamine and LSD 25. Atropine and physostigmine still produced their characteristic effects on electrical activity but did not modify the behavioural state induced by chlorpromazine or methopromazine.

3. Chlorpromazine in doses of 1.5-4.0 mg/kg. produced an increase in the slow waves and spindle activity in the *encéphale isolé* preparation and at the same time made the preparation more difficult to arouse. Smaller doses produced a transient blocking of this activity with the first injection, but larger doses caused a blood pressure fall and flattening of the record. Chlorpromazine had no effect on the *cerveau isolé* preparation other than the effects associated with a fall in blood pressure.

4. The results are discussed in relation to the planes of section of the two acute preparations and the possible sites of action of the other drugs used. It is suggested that chlorpromazine has a depressant action on the brain stem reticular system and that this action may be related to its anti-adrenaline properties. It is further suggested that small doses have an excitatory action which can only be observed before the depressant action has appeared.

We wish to thank Professor J. Elkes for his advice and encouragement, M. Longmore and L. F. Williams for technical assistance, Messrs. May and Baker for providing Methopromazine and Chlorpromazine, and Messrs. Sandoz Products Ltd. for supplies of LSD 25.

REFERENCES

Amin, A. H., Crawford, T. B. B. and Gaddum, J. H. The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *J. Physiol.*, **1954**, *126*: 596-618.

Benditt, E. P. and Rowley, D. A. Antagonism of 5-hydroxytryptamine by chlorpromazine. *Science*, **1956**, *123*: 24.

Bonvallet, M., Dell, P. et Hiebel, G. Tonus sympathique et activité électrique corticale. *EEG Clin. Neurophysiol.*, **1954**, *6*: 119-144.

Boyd, E. M., Cassell, W. A. and Boyd, C. E. Prevention of apomorphine-induced vomiting by (dimethylamino-1-n-propyl-3)-N-(2-chloro)-phenothiazine hydrochloride. *Fed. Proc.*, **1953**, *12*: 303.

Bradley, P. B. Observations on the effect of drugs on the electrical activity of the brain. Ph.D. thesis, University of Birmingham, **1952**.

Bradley, P. B. and Elkes, J. A technique for recording the electrical activity of the brain in the conscious animal. *EEG Clin. Neurophysiol.*, **1953**a, *5*: 451-456.

Bradley, P. B. and Elkes, J. The effect of amphetamine and *d*-lysergic acid diethylamide (LSD 25) on the electrical activity of the brain of the conscious cat. *J. Physiol.*, **1953**b, *120*: 13-14 P.

Bradley, P. B. and Elkes, J. The effect of atropine, hyoscyamine, physostigmine and neostigmine on the electrical activity of the brain of the conscious cat. *J. Physiol.*, **1953**c, *120*: 14-15 P.

Bradley, P. B. and Elkes, J. The effect of some drugs on the electrical activity of the brain. *Brain*, **1956**, in press.

Bremer, F. Cerveau "isolé" et physiologie du sommeil. *C. R. Soc. Biol.*, Paris, **1935**, *118*: 1235-1241.

Bremer, F. Nouvelles recherches sur le mécanisme du sommeil. *C. R. Soc. Biol.*, Paris, **1936**, *122*: 460-464.

Cathala, H. P. et Pocidalo, J. J. Sur les effets de l'injection dans les ventricules cérébraux du chien du chlorohydrate de diméthylamino-propyl-N-chloro-phénothiazine (4560 RP). Action centrale de ce produit. *C. R. Soc. Biol.*, Paris, **1952**, *146*: 1709-1711.

Charpentier, P., Gailliot, P., Jacob, R., Gaudechon, J. et Buisson, P. Recherches sur les diméthylaminopropyl-N-phénothiazines substituées. *C. R. Acad. Sci.*, Paris, **1952**, *235*: 59-60.

Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M. et Koetschet, P. Propriétés pharmacodynamiques du chlorohydrate de chloro-3-diméthylamino-3'-propyl)-10-phénothiazine (4560 RP); étude expérimentale d'un nouveau corps utilisé dans l'anesthésie potentialisée et dans l'hibernation artificielle. *Arch. int. Pharmacodyn.*, **1953**, *92*: 305.

Das, N. N., Dasgupta, S. R. and Werner, G. Changes of behaviour and electro-encephalogram in rhesus monkeys caused by chlorpromazine. *Arch. int. Pharmacodyn.*, **1954**, *99*: 451.

Das, N. N., Dasgupta, S. R. and Werner, G. The effects of chlorpromazine on the electrical activity of the "cerveau isolé". *Arch. exp. Path. Pharmak.*, **1955**, *224*: 248-252.

Delay, J. et Deniker, P. Les neuroplégiques en thérapeutique psychiatrique. *Thérapie*, **1953**, *8*: 347.

Elkes, J. and Elkes, C. Effect of chlorpromazine on the behaviour of chronically overactive psychotic patients. *Brit. med. J.*, **1954**, *ii*: 560-565.

Feldberg, W. and Sherwood, S. L. A permanent cannula for intraventricular injections in cats. *J. Physiol.*, **1953**, *120*: 3-5 P.

Hiebel, G., Bonvallet, M. et Dell, P. Action de la chlorpromazine (Largactil, 4560 RP) au niveau

du système nerveux central. *Sem. Hôp.* Paris, **1954**, *30*: 2346-2353.

KOPERA, J. and ARMITAGE, A. K. Comparison of some pharmacological properties of chlorpromazine, promethazine and pethidine. *Brit. J. Pharmacol.*, **1954**, *9*: 392-401.

LONGO, V. G., VON BERGER, G. P. and BOVET, D. Action of nicotine and of the "ganglioplégiques centraux" on the electrical activity of the brain. *J. Pharmacol. exp. Therap.*, **1954**, *111*: 349-359.

MAGOUN, H. W. The ascending reticular activating system. *Res. Publ. Ass. nerv. ment. Dis.*, **1952**, *30*: 480-492.

MAY & BAKER, LTD. Advance information. **1955**.

MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.

RHEINBERGER, M. B. and JASPER, H. H. Electrical activity of the cerebral cortex in the unanesthetised cat. *Amer. J. Physiol.*, **1937**, *119*: 186-196.

TERZIAN, H. Electroencephalographic study of the central action of Largactil (4560 RP). *Rass. Neurol. veg.*, **1952**, *9*: 211.

VOGT, M. The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. *J. Physiol.*, **1954**, *123*: 451-481.

WASE, A. W., CHRISTENSEN, J. and POLLEY, E. The accumulation of S^{35}-chlorpromazine in brain. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *75*: 54-56.

WIKLER, A. Pharmacologic dissociation of behaviour and EEG "sleep patterns" in dogs: morphine, N-allylnormorphine, and atropine. *Proc. Soc. exp. Biol. N.Y.*, **1952**, *79*: 261-265.

Reference: BRADLEY, P. B. and HANCE, A. J. The effect of chlorpromazine and methopromazine on the electrical activity of the brain in the cat. *EEG Clin. Neurophysiol.*, **1957**, *9*: 191-215.

PRINTED IN CANADA

ANNOUNCEMENT

EXCERPTA MEDICA LIFTS THE CURTAIN ON SOVIET MEDICINE

As a result of plans initiated by the Public Health Service, National Institutes of Health, U.S. Department of Health, Education, and Welfare, arrangements have recently been completed with the *Excerpta Medica Foundation* whereby, for the first time in the history of medicine, an extensive review of the Soviet medical literature in all areas of medicine will now be available to medical science in the United States.

The plan calls for the translation and publication of abstracts of the Soviet medical literature, including reports of the work now being done in various cities throughout the U.S.S.R. The abstracts will be prepared by Soviet specialists most qualified to undertake this work, the material being edited and supervised by Excerpta Medica's own specialist, permanent Editorial Committee of thirty Soviet scientists appointed by the *Excerpta Medica Foundation* in cooperation with the Presidium of the Academy of Medical Sciences of the U.S.S.R. These abstracts will be supplemented by verbatim translations of abstracts of the Soviet literature in specially selected fields.

The abstracts will be published under the title *Abstracts of Soviet Medicine* and will appear throughout 1957 as two separate publications: Part A, *Basic Medical Sciences,* and Part B, *Clinical Medicine,* totalling together some 1300-1400 pages.

The West has long realized that the inaccessibility of so much of the Soviet medical literature has left a great and perhaps vital gap in our knowledge. The primary objective of this far-reaching project is to assist in the creation of the final essential link in the interchange of medical information on a truly global basis.

EFFECT OF ATROPINE AND SCOPOLAMINE UPON ELECTRO-ENCEPHALOGRAPHIC CHANGES INDUCED BY ELECTRO-CONVULSIVE-THERAPY [1]

GEORGE A. ULETT, Ph.D. and MARGARET W. JOHNSON, M.A.
Department of Psychiatry and Neurology, Washington University School of Medicine
and
Research Laboratories of Malcolm Bliss Hospital, St. Louis, Missouri

(Received for publication: July 6, 1956)

There has been considerable speculation about, but little understanding of the significance of the very marked slowing of brain wave activity that characteristically accompanies a course of electro-convulsive treatments. Numerous investigators have pointed out that such slowing is seen in the EEG by the 6th treatment and is most marked in the frontal leads. It progresses in intensity to the 12th - 16th treatment after which, despite more treatments, it remains relatively unchanged only to disappear some 3-6 weeks after treatments are discontinued. Although early attempts to correlate the amount of slowing with clinical recovery were unrewarding (Callaway 1950), it is perhaps more than coincidence that, in affective psychoses, clinical gains are usually seen by the 6th treatment and the maximum amelioration of symptoms is achieved by the 12th-16th treatment. It is also noteworthy that sub-convulsive treatments which produce only evanescent changes in the EEG are without clinical effect. Recently Fink and Kahn (1956) reported a correlation between the degree of EEG slowing and the amount of behavioral change seen clinically.

One way to gain information about the importance of such brain wave slowing would be to administer the convulsive treatments in such a way that the EEG change would be prevented or at least minimized. A method that seemed promising in this regard was suggested by A. A. Ward (personal communication) who has demonstrated that large doses of atropine can, in the monkey, prevent the slowing of EEG patterns that occur with a concentrated application of electrically induced seizures. Ward has also demonstrated that atropine can be safely given to man in doses of 10 mg. daily for amelioration of the symptoms of the post concussion syndrome (1950). Review of the literature revealed that even much larger doses can be safely given to man (Forrer 1951).

The present work is of an exploratory nature, in which we have attempted to see if large doses of atropine would effectively block the EEG slowing in psychiatric patients undergoing a series of electro-convulsive treatments.

METHOD

Atropine sulfate was administered (I.M.) to 7 patients in daily doses ranging from 1-5 mg. The drug was given in two injections, one at 8:00 a.m. and one at 4:00 p.m. Most patients were kept on 5 mg. daily. Five patients received scopolamine hydrobromide in doses of 1-3 mg. administered in similar manner.

In all patients intraocular tension was tested manually and a 4 per cent solution of pilocarpine was instilled in each eye b.i.d.

Both atropine and scopolamine were continued daily, throughout the course of ECT, and in some instances for a few days after conclusion of the convulsive therapy.

EEG's were recorded from scalp to scalp leads, by means of a Gilson 8-channel electroencephalograph. Records were taken before, at intervals during and after concluding the series of convulsive treatments. In most instances the recording was done on the day of

[1] This study was supported by a research grant from the National Institute of Mental Health of the National Institutes of Health, United States Public Health Service.

(3-4 hours after) and on the day following (approximately 24 hours after) the convulsive treatment.

The electro-convulsive treatments were produced by 60 c/sec. sine wave current administered from either Medcraft or Offner equipment.

Six additional patients were selected to match this group for diagnosis and age. They were followed electroencephalographically throughout a course of ECT, administered without atropine or scopolamine.

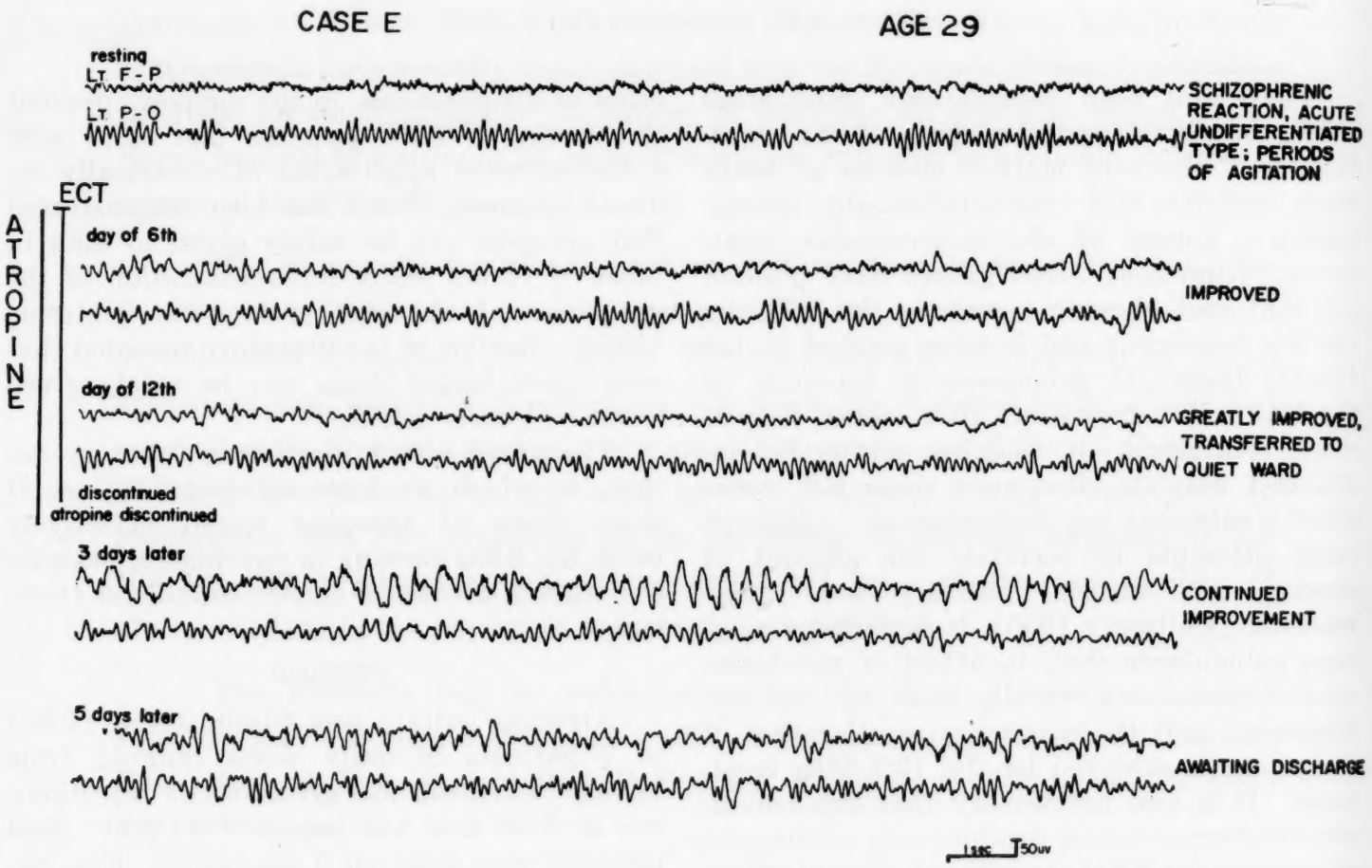


Fig. 1

Samples of EEG tracings taken before and during a series of electro-convulsive treatments. The patient, a 29-year-old woman with schizophrenic reaction received 5.0 mg. of atropine sulfate daily during the treatment series. Her record remained relatively normal until the atropine was discontinued.

RESULTS

A. Atropine

Six patients (mean age 30.4 years) were maintained on atropine sulfate for periods of from 21 to 36 days while receiving electroshock treatment. The highest total daily dosage was 5.0 mg. In one patient 2.5 mg. was the daily dose throughout, in another an initial dose of 2.5 mg. was boosted to 5.0 mg. after 11 days. In a seventh patient the atropine was discontinued on the ninth day due to complaint of chest pain, unexplained by EKG or physical examination.

Pulse and blood pressure measurements on all patients were taken at 15 min. intervals for the first hour after injection and then hourly for 2-3 hours. In this group pulse rates were seen as low as 42 and as high as 147. Changes in blood pressure were seen regularly following atropine administration. A drop of 40-60 points in diastolic or similar rise in systolic was not unusual.

Patients complained of being flushed, dry and sleepy. Some confusion was seen, although psychic symptoms distinguishable from the patient's presenting psychiatric complaints were not readily observed.

Four of the 7 had initially normal EEG's, one showed paroxysmal activity, one was an S_1, and one had a record characterized by mixed fast and slow activity. It was the common experience that while on atropine much less than the anticipated amount of slowing of brain waves following ECT was seen (fig. 1). On some occasions records taken on the day following the 12th treatment seemed entirely normal, more usually a moderate or minimal amount of low voltage slow 4-8 per sec. activity would be present. In no case was there present the high voltage slow activity that is seen in the majority of ECT treated cases. Usually records taken on the day of, and 3-5 hours following convulsive treatment, showed more abnormality than records taken on the day following ECT (fig. 2). In two instances, however, the opposite was seen. When atropine administration was stopped within the first week post treatment, marked slow activity returned in the EEG (fig. 1). If atropine was continually administered during this post shock period, and then stopped, the record remained more nearly normal (fig. 2).

All but one of these patients were diagnosed as having schizophrenic reaction. Two showed marked improvement (including the one patient with involutional psychotic reaction of depressed type). Two showed slight improvement and 3 showed no change in clinical condition following ECT.

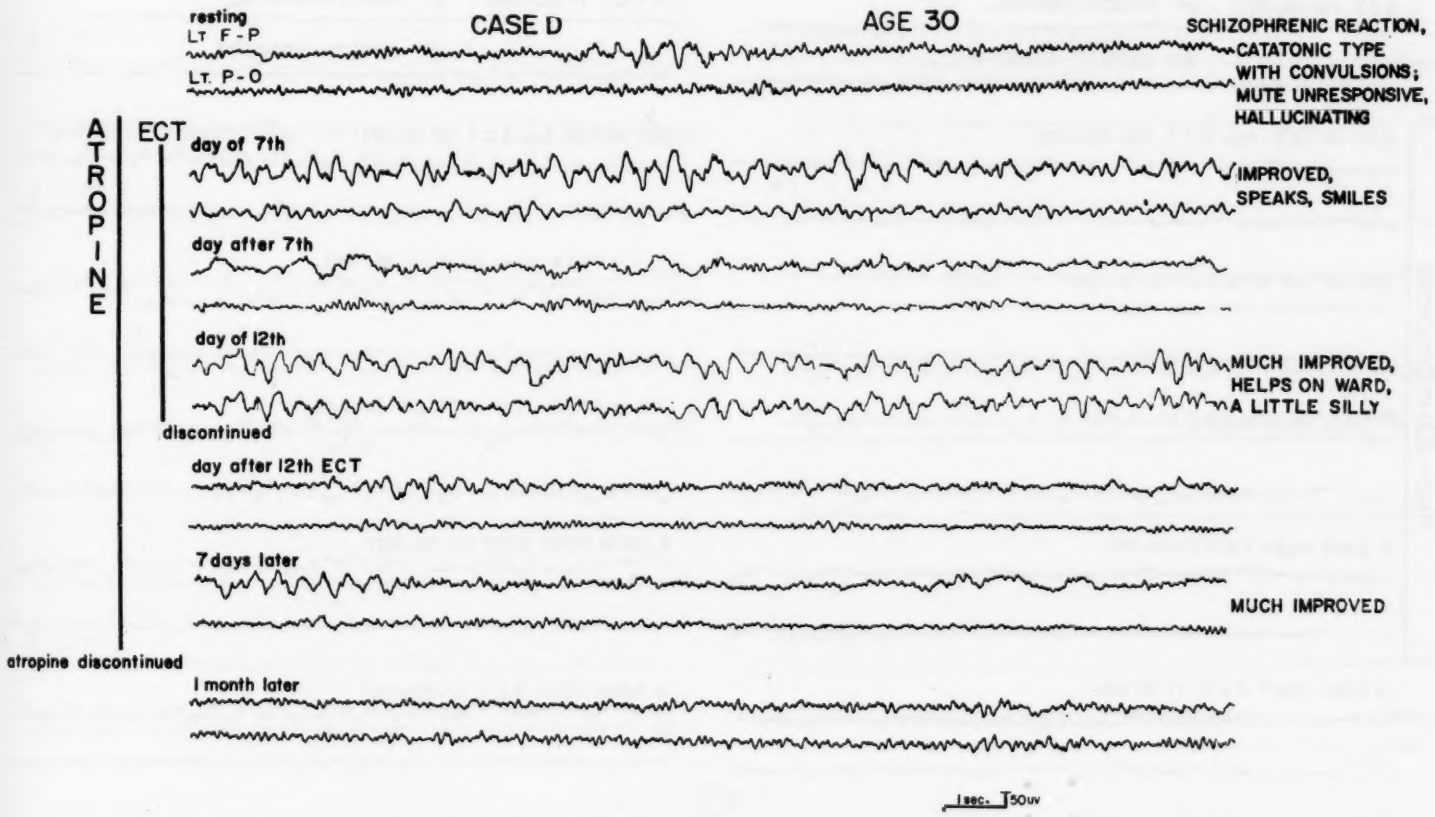


Fig. 2

Representative EEG samples from a 30-year-old woman with chronic schizophrenic reaction. Her resting record shows rare bursts of slow activity. She received 2.5 mg. of atropine sulfate daily for the first 11 days of electro-convulsive therapy and subsequently 5 mg. throughout the remainder of the treatment period and for seven days thereafter. It can be seen that the atropine tended to block the usual slowing of ECT but that such blocking action was least effective on the days when ECT was administered.

B. *Scopolamine*

Scopolamine was administered with some caution to 5 patients (mean age 33.6 years). Two received 1 mg. doses for 4 weeks and 1 received 2 mg. daily for 36 days. One patient received 1 mg. for 16, 2 mg. for 5 and 3 mg. for 9 days, while another received 3 mg. daily for 16 days at which time he

became agitated and the drug was stopped. This latter patient, however, had displayed similar episodic disturbed behavior prior to drug administration. It was our clinical experience that more confusion, excitement and drowsiness resulted from the administration of scopolamine than was seen in the case of atropine. Pulse and blood pressure changes were less marked with these small doses of scopolamine than was the case with atropine.

Four of the subjects had normal resting EEG's, and one had an LVF record. The blocking of ECT-induced, EEG slowing by these small doses of scopolamine seemed to be as good as or better than that seen with larger doses of atropine. Return of slow activity was evident when the scopolamine administration was stopped within a few days after termination of ECT.

Two of the patients in this series showed slight improvement, one was a man with involutional psychotic reaction, depressed type and one was a patient with schizophrenic reaction. The 3 remaining patients were diagnosed as schizophrenic reaction. One of these showed a transient slight improvement, while the other 2 were unimproved by the electroshock treatment.

Two patients were given a second course of ECT. These were begun 12 and 19 days

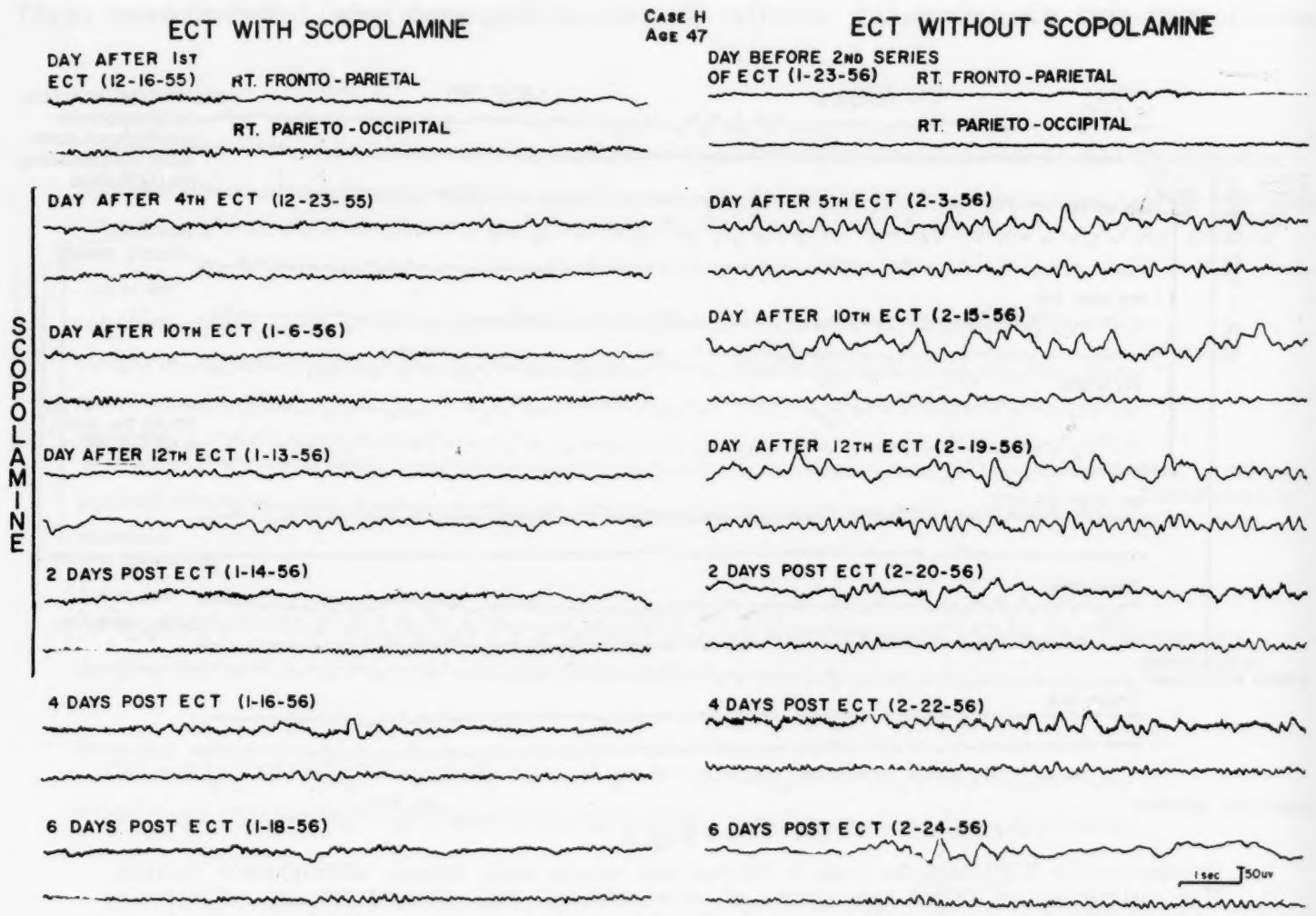


Fig. 3

Representative samples taken from EEG recordings on a 47-year-old man with involutional psychotic reaction. During and for two days after completion of a first series of ECT the patient received 1.0 mg. of scopolamine hydrobromide daily and showed only slight slowing in the EEG. He was given a second series of ECT 27 days later, this time without scopolamine. Marked slowing of the EEG occurred.

after completion of the first course of treatment and at a time when the resting EEG appeared normal. In both of these cases, EEG samples taken at comparable times during and upon completion of the two series demonstrated a more marked slowing of the EEG when scopolamine was not given (fig. 3).

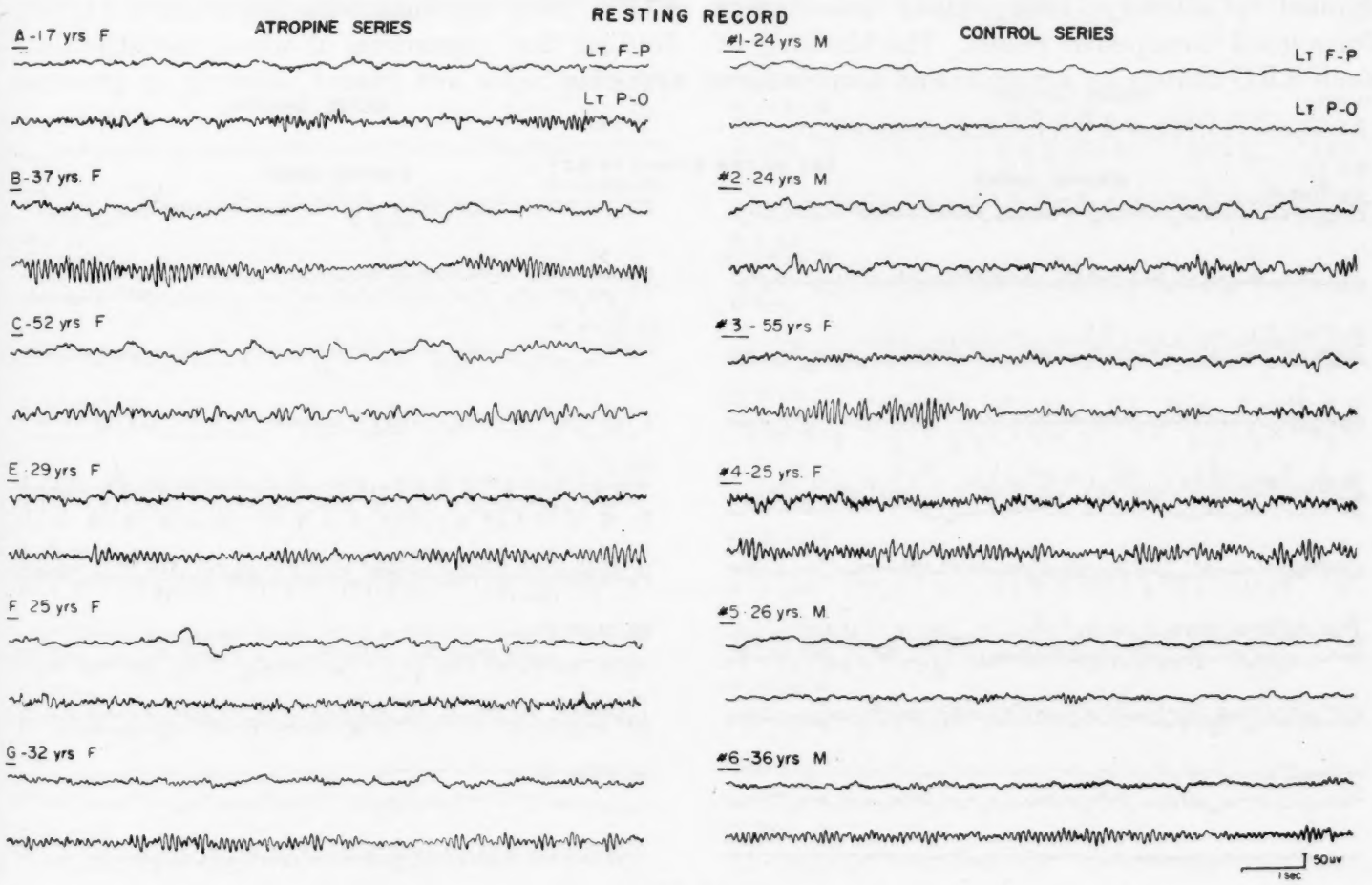


Fig. 4

Representative samples from the resting electroencephalographic records of 12 patients all of whom received a series of 12 electro-convulsive treatments in the ensuing four week period. Those patients listed as the "Atropine Series" received daily injections of atropine-sulfate (2.5-5.0 mg.) throughout the series of treatments, whereas the "control" group did not. (See following figures 5 and 6.)

C. Controls

The first 6 consecutively available patients of similar age (mean 31.6 years) and diagnosis (5 schizophrenic reaction and one involutional psychotic reaction, depressed type) were used for a comparison of EEG's taken during a course of conventional type (sine wave) ECT. Five of these patients had normal resting EEG's, while one showed predominantly mixed fast and slow activity. In all cases the records became markedly slowed by the 6th or 7th treatment, with increasing high voltage activity seen following the 12th treatment and persisting for as long as the patients were followed (i.e., from 12-18 days post ECT). Four of these patients, including the involutional psychotic reaction, showed good clinical results from treatment. A comparison of the records of these control patients with the 6 who received atropine clearly demonstrates the blocking action of this agent (figs. 4, 5 and 6).

DISCUSSION

Of all the physical treatments used in psychiatry, electro-convulsive-therapy has alone

well stood the tests of time, cumulative clinical experience and statistical studies. Its mode of action, however, is still unclear. The dramatic slow changes that occur in the EEG accompanying this treatment, have remained a controversial subject with evidence both for (Fink and Kahn 1956; Roth 1951) and against (Callaway 1950) their essentiality for a good therapeutic result. The blocking of such EEG change by atropine and scopolamine to the therapeutic response, some understanding of how such brain wave changes arise would be of inestimable value to psychiatry. Careful work of Hartelius (1952) and others has demonstrated that only a small minority of the cells of the central nervous system undergo irreversible changes with intensive ECT. This, together with Blaurock's (1950) finding that regardless of where the stimulating electrodes are placed, slowing is greatest

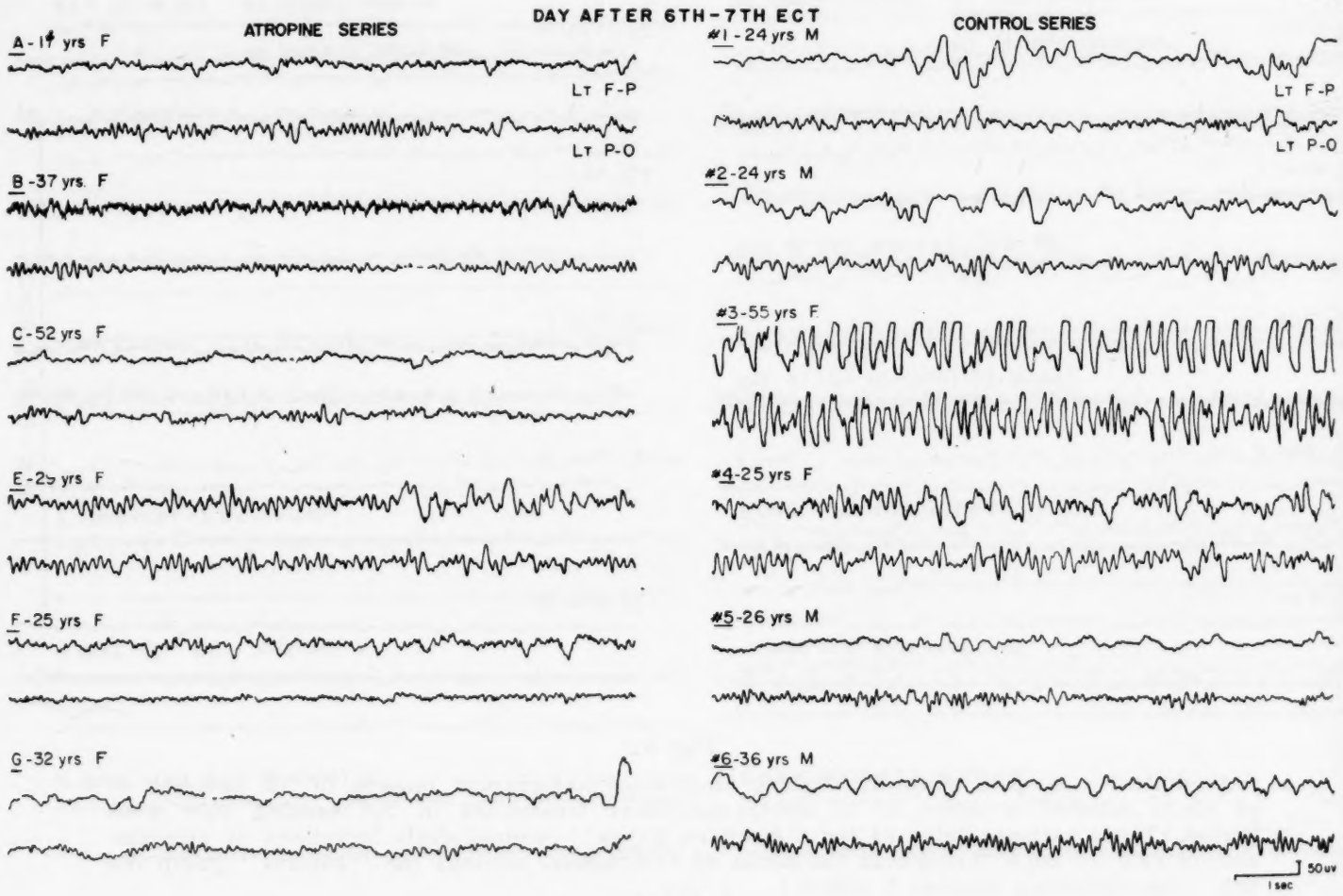


Fig. 5

Representative samples from electroencephalograms taken on the day following the 6th-7th ECT on the same 12 patients illustrated in figure 4. These records show minimal slowing in the atropinized group and marked slowing in the controls.

presents us with a tool to further investigate the hypothesis that EEG slowing is essential for recovery. In the present exploratory study, however, the predominance of patients with schizophrenic reaction and the smallness of the sample, preclude drawing any valid conclusions in this regard.

Whether the slow wave changes in the EEG are directly or only indirectly related in the frontal areas, suggests that the slow waves result from other causes than local cell death or injury. Chusid and Pacella (1952) have stated that the EEG changes seen with electro-convulsive-therapy are related primarily to the intensity of the physiologic or convulsive response. Such an hypothesis finds support from the work of Mills *et al.* (1953) who have shown that the clinically milder

treatments caused by unidirectional currents produce less slowing (and also less clinical improvement) than an equal number of treatments given by conventional sine wave stimulation.

Roth (1951) has postulated that the EEG slowing induced by ECT is actually the result of a change in diencephalic pacemakers which then project a disturbed rhythm to control cortical activity. In favor of this point of view is the fact that, in our investigation, when atropine administration was stopped, the slow activity appeared, with a suddenness and intensity suggesting that it may have been sub-cortically present all the time. On the other hand, it is possible that ECT produced some more generalized neuronal change whose presence was detectable only when synaptic transmission was normal so that during atropine administration the slow brain waves could not be seen. Scopolamine, which is reputed to exert an even greater central effect, served to block the slow activity, of whatever origin, to a more marked extent even with the relatively smaller doses used in our series.

Further studies are needed both in animals and in humans to clarify such questions as to the site and mode of action within the brain of atropine, scopolamine and electro-convulsive therapy.

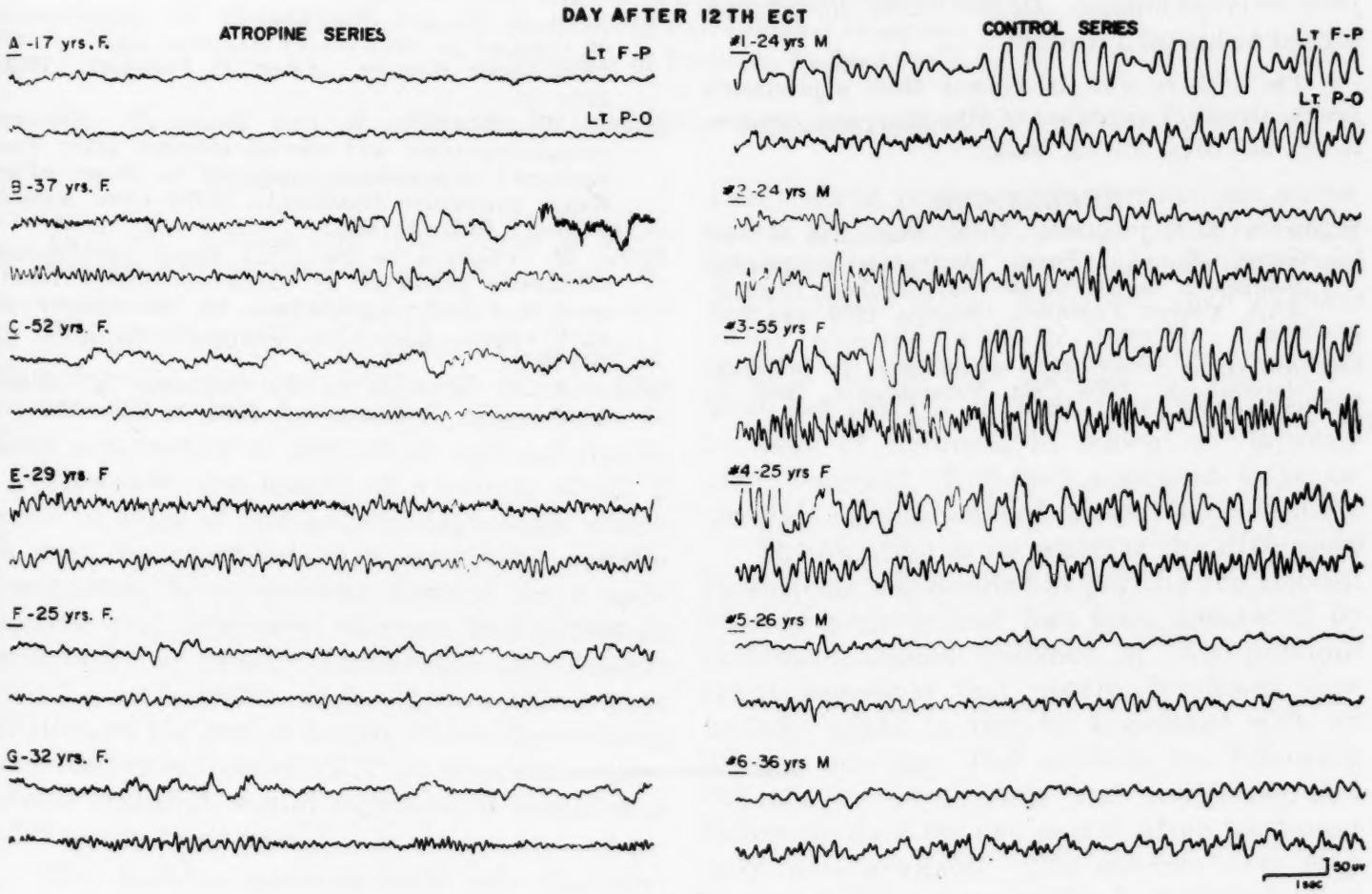


Fig. 6

Representative samples from electroencephalograms taken the day following the 12th electro-convulsive treatment in the group of 12 patients illustrated in figures 4 and 5. These records clearly demonstrate the blocking effect of atropine upon slow activity produced by electro-convulsive treatment.

SUMMARY

An investigation was made of the effects of daily administered 1-5 mg. doses of atropine and scopolamine, upon the alteration of brain wave pattern that characteristically accompanies a course of electro-convulsive treatments. Both of these agents clearly

blocked the occurrence of slow waves usually seen following ECT. In cases where the drug was continued for a week or more after termination of ECT, marked slowing did not occur. If the drug was discontinued within 1-2 days after the course of treatment, slow high voltage activity would suddenly appear.

Comparison was made with the EEG's of other persons who received ECT without atropine or scopolamine. In two cases the patient served as his own control.

The authors wish to express their appreciation for the technical assistance of Miss Margaret Johnson, R. N., and Mrs. Phyllis Drake.

REFERENCES

BLAUROCK, M. F., LORIMER, F. M., SEGAL, M. M. and GIBBS, F. A. Focal electroencephalographic changes in unilateral electric convulsion therapy. *Arch. Neurol. Psychiat.*, Chicago, **1950**, *64*: 220-226.

CALLAWAY, E. Slow wave phenomena in intensive electroshock. *EEG Clin. Neurophysiol.*, **1950**, *2*: 157-161.

CHUSID, J. G. and PACELLA, B. L. The electroencephalogram in the electric shock therapies. *J. nerv. ment. Dis.*, **1952**, *116*: 95-107.

FINK, M. and KAHN, R. Quantitative studies of slow wave activity following electroshock. *EEG Clin. Neurophysiol.*, **1956**, *8*: 158.

FORRER, G. R. Atropine toxicity in the treatment of mental disease. *Amer. J. Psychiat.*, **1951**, *108*: 107-112.

HARTELIUS, H. Cerebral changes following electrically induced convulsions. *Acta Psychiat. Neurol. Scand. Suppl.* 77, Ejnar Munksgaard, Copenhagen, **1952**.

KENNARD, M. A. and WILLNER, N. D. Significance of changes in electroencephalogram which result from shock therapy. *Amer. J. Psychiat.*, **1948**, *105*: 40.

MILLS, W., KENDALL, B. and THALE, T. Electroencephalographic and mental changes after conventional electroshock compared to those after Reiter convulsive treatments. *EEG Clin. Neurophysiol.*, **1953**, *5*: 480.

ROTH, M. Changes in the EEG under barbiturate anesthesia produced by electro-convulsive treatment and their significance for the theory of ECT action. *EEG Clin. Neurophysiol.*, **1951**, *3*: 261-280.

WARD, A. A. Atropine in the treatment of closed head injury. *J. Neurosurg.*, **1950**, *7*: 398-402.

Reference: ULETT, G. A. and JOHNSON, M. W. Effect of atropine and scopolamine upon electroencephalographic changes induced by electro-convulsive therapy. *EEG Clin. Neurophysiol.*, **1957**, *9*: 217-224.

PRINTED IN DENMARK

PROGNOSIS AND PENTOTHAL INDUCED ELECTROENCEPHALOGRAPHIC CHANGES IN ELECTRO-CONVULSIVE TREATMENT

An approach to the problem of regulation of convulsive therapy

MARTIN ROTH, M.D., D. W. K. KAY, B.M., JOHN SHAW, B.Sc.
and JOY GREEN

Department of Clinical Research, Graylingwell Hospital
and Department of Psychological Medicine,
University of Durham, England

(Received for publication: September 10, 1956)

INTRODUCTION

It is well known that if a course of ECT is interrupted as soon as symptoms are observed to be in abeyance, relapse will occur in a high proportion of cases. It is usual, therefore, to continue treatment beyond this point, which may be reached after three to four treatments, to achieve an optimal result.

However, the length of a course of ECT even in cases of endogenous depression where it may be regarded as a relatively specific treatment, is at present decided in a subjective and arbitrary manner, and although prognosis is usually favourable the relapse rate is undesirably high. Any method that prolonged the period during which the striking qualitative effects of ECT on depressive psychosis endured, would represent a significant advance in treatment.

The problem resolves itself into discovering a measure of the changes produced by ECT in the brain that is more objective than the existing procedure of ascertaining the effects clinically as treatment proceeds, and susceptible of description in precise quantitative terms. It might then be possible to ascertain whether in a given condition effective courses of treatment had consistent physiological correlates. If they did these might serve as a basis for development of the optimal technique.

In previous papers (Roth 1951, 1952) it has been shown that although the ordinary EEG may fail to reveal changes during or even after therapeutically effective courses of ECT (a fact previously demonstrated by other authors, e.g. Moriarty and Siemens 1947), serial studies under barbiturate anaesthesia will consistently uncover EEG changes at an earlier stage of treatment than the record in the awake state. Moreover, such changes either coincide with or precede the first signs of clinical improvement. These changes were not specific in that they were present in cases of neurosis, in which no improvement occurred. But they appeared to be invariable concomitants of clinical improvement.

The question arose whether the difference in outcome was decided in part by the amount of slow activity that had been generated by treatment. Some evidence in this previous study suggested that poorly developed slow activity might in fact be associated with an adverse outcome. But methods for following the change were crude and subjective and follow-up data for one month after treatment only were available. The obvious next step was to develop some method of quantitative assessment of the amount of slow activity and to see whether the measure of this was correlated in any way with outcome.

The findings in this paper suggest the lines along which such a method might be developed, in that they indicate that in endogenous depression the outcome is markedly influenced by the peak value of slow activity as measured in the Pentothal record by a special technique. The practical significance of such a finding lies in the fact that within limits the quantitative severity of this slow activity can be influenced by varying the number of convulsions and their spacing. The findings also have some interesting theoretical implications for the problems of mode of action of convulsant treatment.

MATERIAL AND METHOD

The material consisted of 41 patients with psychotic depression. Only cases of unequivocally endogenous type were included, all of them with depression of psychotic depth relatively sharply defined in time of onset and with at least two of the following features in addition; early morning awakening, diurnal variation in mood, retardation or stupor, ideas of guilt and self reproach, nihilistic ideas or paranoid ideas of depressive type. To have included first admissions only would have restricted the numbers severely, but a clear remission for a period of at least 18 months preceding the present attack was made a criterion for inclusion in the investigation. Twenty-nine of the cases were in fact first attacks. In such cases of endogenous depression the prognosis for ECT is generally favourable. Failures are sometimes recorded or only a short-lived response elicited, but the reasons for this are unknown, nor is there any reliable way of identifying such potential failures before the administration of treatment.

In the hospital where most of this work was carried out, ECT was administered either in set courses of 6 or 7 convulsions or treatment was continued until it was judged clinically that an optimal stage had been reached. The investigation had to be adjusted to these patterns of ECT administration, each being favoured by some of the clinicians in charge of the cases. Accordingly two groups of cases receiving set courses were studied; one of 10 cases given 6 treatments and another of 14 cases given 7 treatments. A third group of 18 cases contained those that had been given courses of varying length judged to be optimal on clinical grounds. The spacing of treatments was identical for each case. Three treatments were always given on alternate days during the first week while in the remainder of the course they were administered at the rate of two per week.

Although the number of ECT could not be kept constant there were enough cases in each group for conducting a preliminary investigation into the part played by slow activity in giving rise to differences in pattern of outcome.

CLINICAL ASSESSMENT

A detailed clinical assessment of each patient was made before commencement of ECT and within the first three days after the termination of treatment. Clinical progress was recorded daily by one of us in 14 of the cases, in 16 others a daily record sheet was kept by other members of the medical staff and in 12 patients progress was described on behaviour charts by members of the nursing staff. It became clear after the investigation had been in progress for 18 months, during which 26 cases had been studied, that the majority of the cases of endogenous depression were in remission immediately after treatment, and that in none of them did some measure of symptomatic improvement fail to occur. But this improvement was sometimes very short-lived. Detailed information about relapse was then sought and in the cases already studied it had to be obtained retrospectively. Examination of the records showed that some patients had not been discharged owing to insufficient improvement or relapse; others had been readmitted or referred for out-patient consultations. Most of these cases were given further ECT and it was possible to ascertain the date of relapse to within a week or two from the case notes. The remaining cases were followed up by home visits, or where this was impracticable, follow-up letters to the nearest relative. Fifteen cases whose investigation was begun after inquiries into relapse rate were initiated were followed up in an out-patient clinic or by postal enquiries at 3, 6 and 12 months. Some relapses may have been undetected but this could have applied to few producing obvious or severe disability. In stating the results at 3, 6 and 12 months, all relapses were counted, whether or not they had meanwhile been brought to remission with further ECT, the principle aim of the investigations being to evaluate the efficacy of the initial course of ECT in promoting stable recovery.

EEG MEASUREMENTS AND RESULTS

1. *Changes in the thiopentone record during treatment.*

An EEG was recorded before treatment and within the fourth hour after each convul-

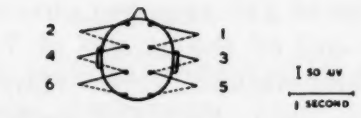
sion in every case. Following completion of the course a record was taken once weekly for three weeks; in a few cases it was possible to continue for longer. After 5 min. ordinary recording the effect of 3 min. overbreathing was studied in most cases. Five per cent thiopentone was then injected at a rate of 1 cc. in 15 sec. with 5 sec. pause between successive cc. When the patient closed his eyes and deep regular breathing began (this occurred after 0.2-0.25 g. in most cases) a further cc. was given at the same rate. With this technique it was found that the dose required in a given patient varied little on successive occasions. The previous techniques failed to produce unconsciousness in a consistent manner and were abandoned since loss of consciousness is an essential condition for the appearance of slow activity.

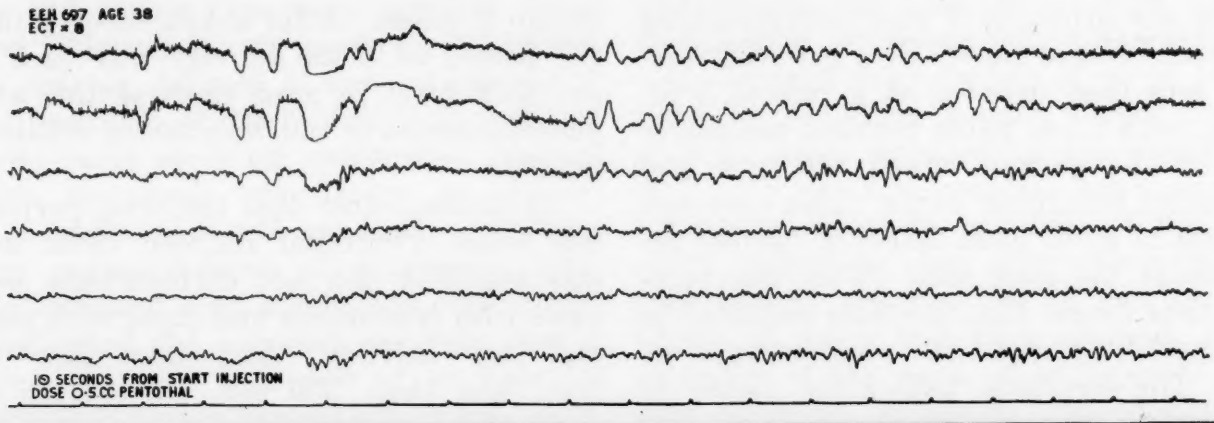
The method of measurement to be described was based upon the observation that the delta activity evoked in a given experiment by such an injection of thiopentone during a course of convulsive treatment has a finite duration (Roth 1951), the end point being marked by a well defined interruption of the rhythmic slow activity which is succeeded by low voltage fast waves (fig. 1). This fast activity is the usual pattern for light barbiturate sleep and it continues without return of the high-voltage slow activity described above, during the whole of the remaining period for which the patient is unconscious. However, sensory stimuli during the first 5 to 20 sec. following this end point may re-evoke a burst of slow activity; this is particularly prone to occur after five to six convulsions have been administered. To avoid this source of variability consistently quiet conditions in the laboratory are essential.

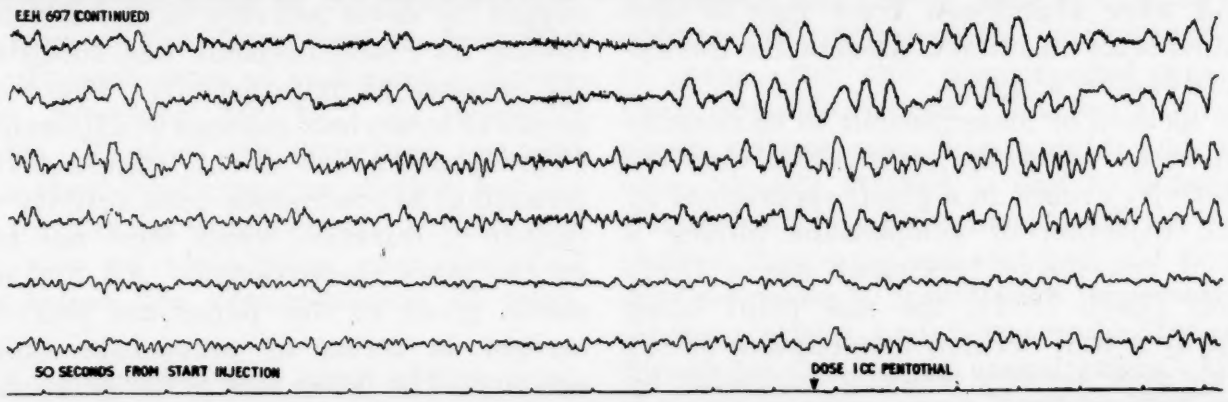
If all delta waves of an amplitude of 50 μV. or above are reckoned, about 40 per cent of cases show a few brief low voltage bursts with an interval of 15 to 20 sec. between the commencement of the first, and the end of the last, slow wave. With successive convulsions there is a progressive prolongation of the length of the period during which slow activity is manifest and if this is plotted against the number of ECT, the rising curve shown in figure 2 is obtained for duration of thiopentone induced delta activity. It will be seen that a peak value of 250 sec. was obtained in this case at the end of the course of 7 treatments. After termination of the course the value fell to less than half the peak value within 3 weeks. After a two months interval the period of delta activity was back to its pre-ECT level in most cases of this and the previous series in which extended studies were possible.

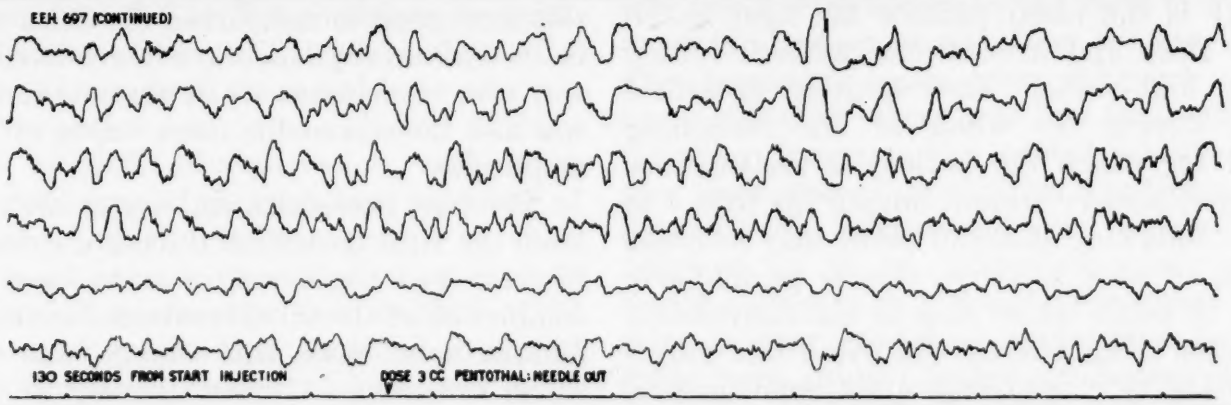
It became clear that the total period during which Pentothal induced delta activity was manifest did not differentiate between cases with continuous and those with paroxysmal slow activity. And since this usually lasts less than 300 sec. in courses of 12 convulsions or less, percentage of time occupied by delta activity in the 300 sec. following its commencement was substituted as the measure of delta activity. This was more sensitive to obvious changes at different stages of one course, such as the transition from intermittent to continuous delta activity without change of duration which were not reflected by the other measurement. All the measurements given in this paper are therefore described in terms of percentage time delta activity. The latter was reckoned in whatever part of the head it appeared, but in practice this amounted to measuring the delta activity in the frontal regions, since it was hardly ever active in other areas when absent there. This was also the site of the delta waves of highest amplitude.

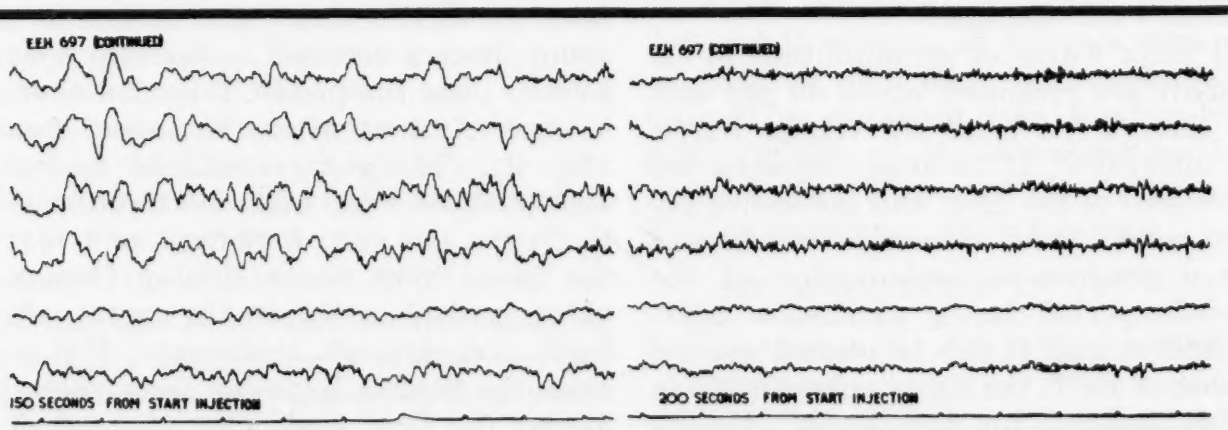
Per cent time delta activity shows changes from the first treatment during a course. An increase was registered in every case by the completion of the third treatment in this series and in most cases this change was evident after the second. Paradoxically in a few cases the effect of the first treatment was to bring about a decrease in per cent time delta activity; but the pre-ECT level was exceeded in each of these after the second treatment (fig. 3). The curve continues to rise with successive ECT but after 8-9 treatments tends to flatten out onto a plateau and in two of the cases there was a decline from a peak value reached earlier in the course, after the tenth and eleventh treatments. But in most cases the decline from the peak value begins during the first week after the end of ECT and the curve then falls steeply to a point


2
4
6
1
3
5
50 uv
1 SECOND


EEH 697 AGE 38
ECT = 8
10 SECONDS FROM START INJECTION
DOSE 0·5 CC PENTOTHAL


EEH 697 (CONTINUED)
50 SECONDS FROM START INJECTION
DOSE 1 CC PENTOTHAL


EEH 697 (CONTINUED)
130 SECONDS FROM START INJECTION
DOSE 3 CC PENTOTHAL: NEEDLE OUT


EEH 697 (CONTINUED)
150 SECONDS FROM START INJECTION
EEH 697 (CONTINUED)
200 SECONDS FROM START INJECTION

still well above the pre-treatment level after three weeks. Only in a few cases were we able in this series to continue studies under thiopentone beyond this point, but from these as well as from previous material studied it would appear that the Pentothal induced slow activity is back to the pre-ECT level within 7 to 9 weeks after a course of 6 to 7 ECT.

Nevertheless the Pentothal record proves to be the more sensitive measure of the changes occurring in the brain during and after treatment and some measurable change is invariably present in it at the time or before the first changes in clinical picture are recorded, in contrast with the ordinary EEG which begins to alter several ECT later (fig. 2, 3).

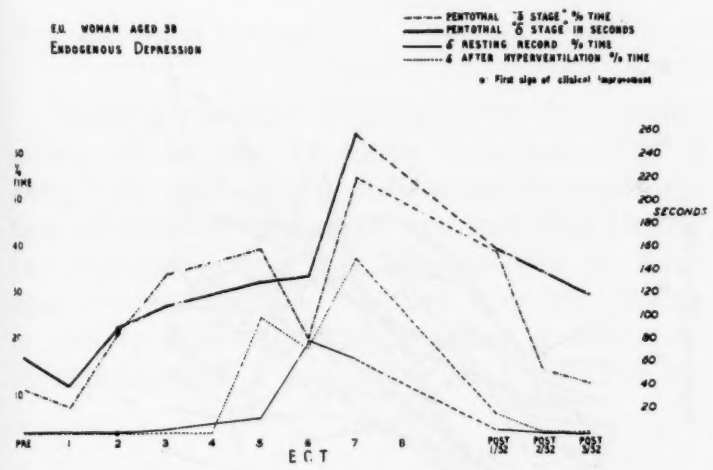


Fig. 2

Both forms of measurement of thiopentone induced delta activity are shown. The curves in this case are similar and both show an earlier change than that detected in the ordinary recordings.

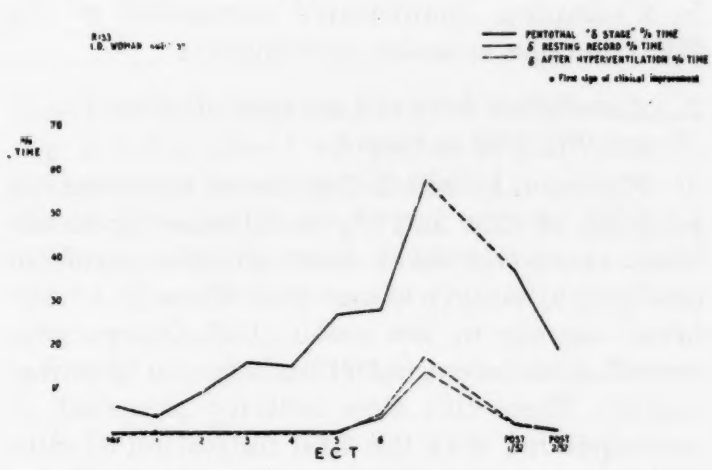


Fig. 3

Changes in percentage time delta activity in resting record, after hyperventilation and after thiopentone injection during an ECT series. A detectable change in the Pentothal record precedes that in the resting record by 5 ECT in this case.

As previously shown (Roth 1951) the Pentothal induced slow wave change anticipates by from 2 to 5 ECT any discernible alteration in the ordinary record and the discrepancy is little less marked when the comparison is with the record during the 300 sec. after hyperventilation (fig. 2 and 3). In only one instance in this material were the changes in the awake and anaesthetized state simultaneous. The curve showing the progress of slow activity in the awake state rises steeply once slow activity has begun and very soon the delta waves are to be seen throughout the record in spasmodic bursts of increasing duration and frequency and not, as in the Pentothal record, during a limited period only.

The technique described here takes no account of certain other changes. One is the appearance in many cases of rhythmic theta waves at 50 to 100 μV. for 5-15 sec. before the run of delta activity begins and for short intervals afterwards. Another is the augmentation of the second component of the K-complex after 5 to 6 treatments (Roth, Shaw and Green 1956); the response may eventually change to a prolonged burst of slow waves with the sharp wave component inconspicuous. There is also an increase in amplitude and rhythmicity of the delta activity and in its differentiation from background activity. All these changes appear later or less consistently

Fig. 1

Thiopentone induced delta activity elicited 3 hours after the eighth ECT. A large part of the delta stage is shown in extracts from the record. Frontally preponderant delta waves began at 10 sec. from the commencement of the upper strip of record. It is intermittent until just before completion of injection of 1 cc., thereafter it is continuous apart from short intervals until 150 sec. from the start of the injection when it is once again intermittent. At 200 sec. from the start, the slow activity is completely in abeyance and barbiturate fast activity dominant. 10 per cent thiopentone was used in this early experiment; the injection technique described in the text had not yet been established.

than the slow wave activity and lend themselves less well to measurement; they are less satisfactory therefore as a basis for the evaluation of the cerebral effects of ECT. There may also be more subtle changes in both ordinary and Pentothal records not to be revealed without a frequency analyzer which it is hoped to utilize in future studies. The possibility of including all such phenomena in a complete quantitative assessment of the EEG changes is under examination.

2. *Association between amount of slow activity and outcome.*

Figure 4, in which the curves representing progress of slow activity in 20 cases up to the sixth treatment have been superimposed on one graph, clearly shows that there is a very broad scatter in the amount of change generated in different individuals for an identical course. Since this slow activity preceded or corresponded with the first indication of clinical improvement, it was pertinent to enquire whether this wide range of EEG effects bore any relationship to differences in outcome.

The peak value of each curve was the measurement chosen as a basis of comparison since it is this that most clearly reflects the cumulative effect of treatment, the assessment of which on the clinical plane determines the regulation of the length of a course of ECT in current clinical practice.

Of the 41 patients, 37 were judged within the 3 days following the end of treatment to have recovered completely or to have achieved a remission with only minor residual symptoms. In the remaining 4, treatment had left the illness essentially unaltered, but some isolated symptom such as anorexia or insomnia had changed in each case for the better and these cases have therefore been classed as improved. The mean of the peak values of these 4 cases (25.7 ± 5.5) per cent time delta is considerably below that for the 37 recovered patients (41.0 ± 14.6) but the difference is not significant. Moreover the actual peak values in the failures were 19, 25, 24 and 34 and in a considerable number of patients in whom recoveries were registered at this stage the peak values fell within or below this range. The relationship between *outcome immediately following treatment* and the peak value of Pentothal induced delta activity is not therefore a striking one.

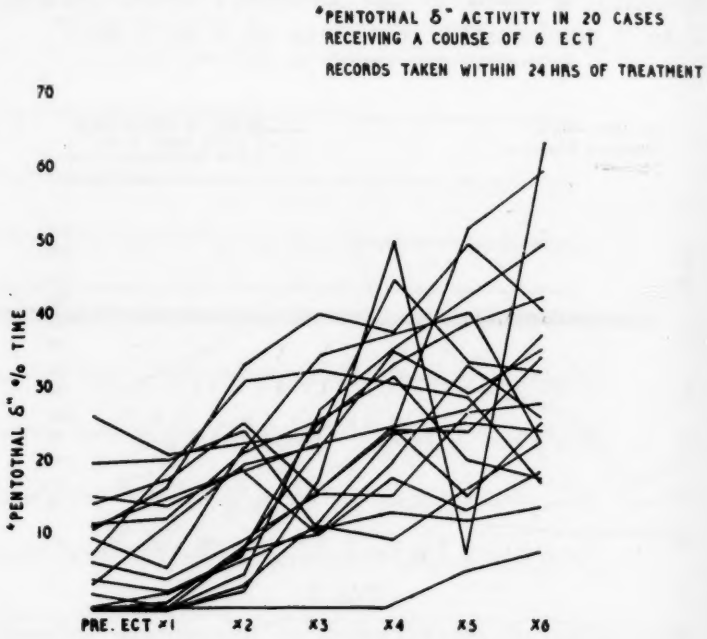


Fig. 4

A very wide range of variation is shown in the rate of change of thiopentone induced slow activity and the peak values attained in these 20 cases.

TABLE I

Pentothal induced slow activity and outcome.

Peak Value % Time Delta, Pentothal record	Number Relapsing	Number Not Relapsing	X^2	*d f*	P
3 Months					
11 — 40	11	11	9.86	1	< 0.01
41 — 50	1	18			
6 Months					
11 — 40	13	9	10.36	1	< 0.01
41 — 50	2	17			

TABLE II

Outcome and thiopentone induced delta activity.

Outcome	Number of Cases	Mean of Peak Value % Time Delta	*f*	N	*d f*	P
Relapsed at 3 months	13	29.2 ± 13.96	3.27	41	39	< 0.01
Not relapsed at 3 months	27	44.75 ± 13.75				
Relapsed at 6 months	16	31.44 ± 14.39	2.909	41	39	< 0.01
Not relapsed at 6 months	24	45.22 ± 13.57				

During the first 12 weeks after their treatment, 12 of the 41 cases relapsed. The 4 cases who had shown only a slight amelioration of isolated symptoms are included among the relapses since this change was in each case reversed within the first 3 weeks. There is clearly a relationship between a tendency to relapse and a low value of Pentothal induced slow activity (table I). Of those attaining a value above 40 per cent only one in 19 relapsed as compared with 11 relapses in 22 cases among those 40 per cent or below, a difference significant at below the one per cent level. The differences are equally striking when relapses in the two groups are compared at six months. There is also a significant

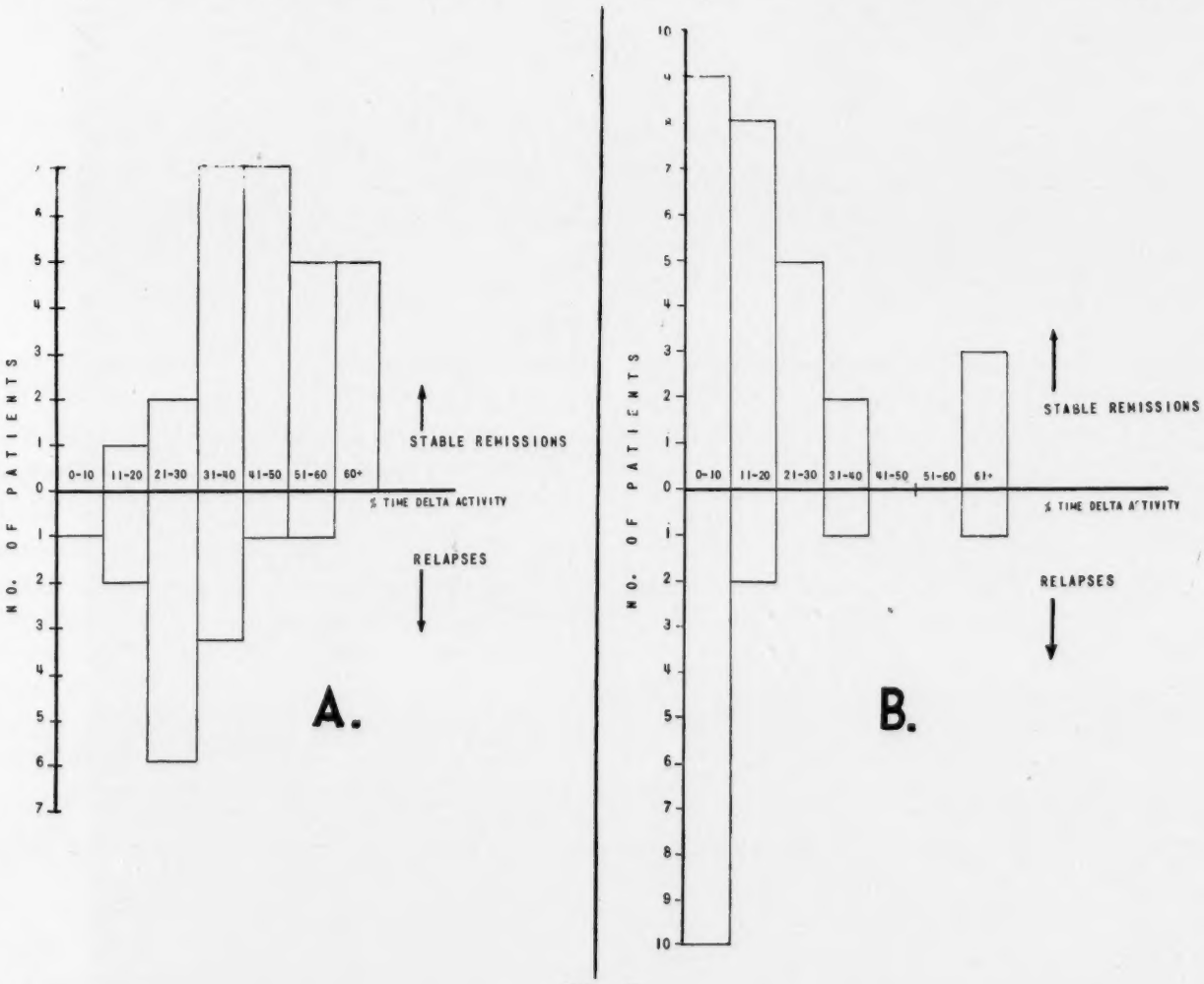


Fig. 5

A. Peak value of thiopentone delta activity in relapsed cases and stable remissions 4½/12 after treatment.

B. Peak value of per cent time delta activity in resting record in relapsed cases and stable remissions 4½/12 after treatment.

difference in respect of the mean peak value of per cent time delta activity between relapsed and not relapsed cases (table II).

The differentiation as between relapsed cases and those remaining in stable remission is evidently less clear cut when the EEG findings in the ordinary record are examined. It will be seen (fig. 5 A) that the overlap between the relapsed and stable cases in relation to their score for thiopentone slow activity is small. The columns to the right of a line at 30 per cent include all but 3 stable recoveries at 4½ months and only 5 of 14 relapses. But for slow activity in the ordinary record (fig. 5 B) almost a third of stable recoveries attain a figure under 10 per cent and so do almost two thirds of the relapses. Four of the stable cases attain figures of 63, 64, 69 and 43 per cent in the thiopentone record which were within or well beyond the range of figures associated with the majority of stable recoveries, although their scores in the resting EEG, 0, 4, 0 and 2 per cent indicated no change or a very slight one. Such cases might well receive a course far in excess of what is needed for stable recovery if treatment were guided by the ordinary EEG alone.

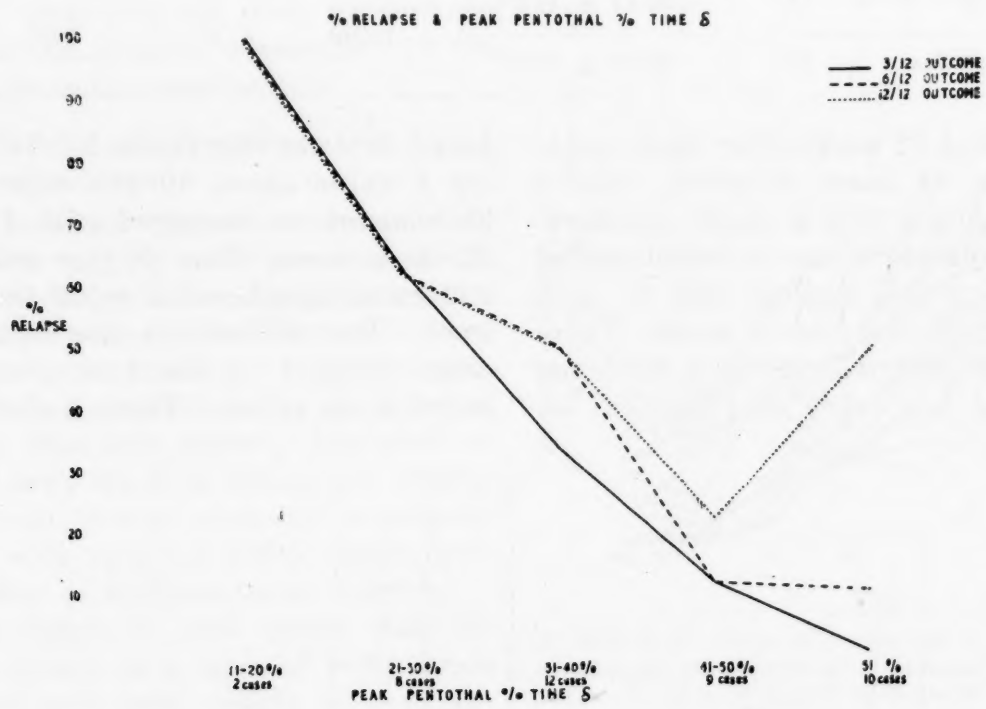


Fig. 6

When percentage relapse is plotted against per cent time delta activity given at 10 per cent intervals on the abscissa, it is seen (fig. 6) that the relationship between them at 3 months after completion of treatment is al-

TABLE III

No. of ECT	No. of Patients	Per cent time delta activity ⩾ 41		Per cent time delta activity ⩽ 40	
		Relapsed	Not Relapsed	Relapsed	Not Relapsed
5	5	0	3	1	1
6	10	0	5	3	2
7	13	2	5	4	2
8	3	0	1	1	1
9	5	0	2	2	1
10	2	0	0	1	1
12	3	0	1	1	1

most linear. A similar curve describes the relationship at 6 months. But after 12 months the situation is more complex, cases with values over 51 per cent showing a higher relapse rate than those in the 41 to 50 per cent range. However, following such an interval many factors other than the physiological effects exerted by the course of ECT have come to influence the result.

In these calculations cases given varying number of ECT were combined but the trend is consistently towards higher relapse rates in those with low values for delta activity irrespective of the number of ECT (table III).

The possibility that the differences in outcome might be due to variables is excluded by a comparison of the groups with peak values of above and below 40 per cent time delta activity which shows them not to differ significantly in respect of mean age, duration of symptoms before treatment and the number of individuals who had suffered previous attacks. Twenty-nine of the 41 cases were in fact suffering from first attacks, but the differences in relapse rate were clearly in the same direction among these cases as in the group as a whole with no change in level of statistical significance.

DISCUSSION

1. *Practical implications.*

The findings indicate that the immediate result of the use of ECT in the majority of cases of depression is good and that the amount of Pentothal induced delta activity has only a small bearing on this result. But a substantial proportion of the remissions thus induced proves unstable and the incidence of relapse is markedly influenced by the EEG changes as measured by the technique described. The practical significance of the findings lies in their promise for the development of a method of quantitative assessment of the effects of convulsive treatment on the brain which will enable the therapist to regulate the course so as to reduce the risk of relapse to a minimum. For the peak value can be varied within limits, by adjusting the number and spacing of the convulsions. This was in fact done in some of the relapsed cases in the present series. A second course with an increased number of treatments more closely spaced in the second week brought the peak value of Pentothal induced slow activity to a higher level than in the initial course in 2 cases who had relapsed in under 3 months; in one a stable remission was induced, in the other, one which lasted 10 months. Unfortunately it was not possible to carry out any more studies in relapsed cases.

The EEG changes are not a correlate of the improved mental state as such. In many schizophrenics qualitatively identical changes may be induced with peak values above the range of 40 to 50 per cent that proved adequate in the majority of depressives with little or no change in the great majority of cases. In neurotics we have studied, similar values have been attained without clinical benefit and it is clear from the experience of a great many workers that ECT is valueless in this group of disorders. Even in endogenous depression it is not recovery as such that is being portrayed by the changes. Thus in one of the relapsed cases a more intensive course produced a peak value of 55 per cent in the Pentothal induced slow activity and this was associated with some degree of confusion, but the only change in the depressive psychosis was a transient improvement in appetite.

The relationship between recovery and the EEG changes is thus an indirect one. The latter seemingly tends to promote recovery by impeding in some way the physiological processes underlying the psychotic illness. But the EEG changes alone do not ensure success; this evidently depends in the first place upon whether or not these physiological processes are susceptible of alteration by convulsive treatment. Neuroses cannot be so influenced and no amount of EEG change would appear materially to affect the issue. Endogenous depressions can respond, on the other hand, and the results described suggest that the EEG changes may serve to indicate whether or not a quantitatively adequate physiological basis for recovery has been provided by treatment.

The optimal value for the change in endogenous depression cannot be stated with precision until further investigations have been carried out. The method has an error of about 5 per cent and above 55 per cent, confusional states were rather common in this series; this

complication should be avoided as far as possible. In the light of the results described it would seem advisable to aim in endogenous depression at producing a peak value of 35 to 50 per cent time delta activity in the Pentothal record. The results show that under 35-40 per cent the change in the brain is quantitatively inadequate to promote stable recovery. In the majority of cases in which figures were below this value, further courses of treatment were necessary and the number of ECT administered may in the end have been in excess of what would initially have proved adequate. However, for the present the figure between the values of 35 and 50 per cent at which treatment is to be brought to an end must be left to an all-round clinical assessment which would take account of such factors as the residual features of the psychosis, any evidence of confusion or intellectual impairment, changes in the patient's physical status, sleep, appetite, etc. If no appreciable clinical change has been observed after a peak value of 45 per cent has been attained, success will rarely follow from proceeding further with the treatment. It should be possible to give more precise guidance as to the optimal value of Pentothal induced slow activity when a larger material has been studied and the influence of age, occurrence of previous attacks, etc., can be evaluated in detail.

The technique as described is too cumbersome for routine clinical practice. But although a Pentothal EEG was essential before therapy and after each convulsion in these investigations, it is unnecessary for any tentative application of the findings as far as they have gone. With the spacing in this series no patient achieved a value of 35 per cent before the fourth treatment. A Pentothal EEG after this and subsequent treatments within 3-4 hours of termination of the convulsion should make it possible to bring the peak value to within the range of 35 to 50 per cent. Another possible application would be to use the technique as a check on the adequacy of a course of treatment judged to be optimal on clinical grounds. A value of 35 to 40 per cent would confirm the clinical impression, but below this further treatment may be indicated.

Clinical observation suggests that the cumulative physiological change by means of which ECT promotes recovery in the brain is a function of the number of fits and the intervals between them. Thus it is well known that if successive ECT are separated by long time intervals, treatment will usually fail. Six ECT given at monthly intervals will produce no change, or only a trivial one, in the clinical picture of involutional melancholia. Further, whereas 2 ECT will promote a transient change or no alteration, 8 ECT given in 3 weeks will induce full remission in a high proportion of cases. The EEG changes as evoked under Pentothal are influenced in a similar manner by these variables of number and spacing of convulsions; the fewer and more widely spaced the treatments, the less the amount of slow activity, for courses of less than ten convulsions, at any rate. The suggestion that there is an intimate association between these EEG changes and the alterations in the brain tending to promote recovery receives further support from the facts to be discussed in the next section.

THEORETICAL ASPECTS

The operation of a quantitative principle in deciding the efficacy of a course of ECT is reminiscent of a similar situation in relation to prefrontal leucotomy. Here the work of Meyer has conclusively shown that the number of thalamo-cortical fibres cut exerts a decisive influence upon the chances of recovery. Inadequate lesions are strikingly prone to be associated with a poor result (Meyer and Beck 1954). And it is of some interest that this failure is often due to a relapse of the mental illness following a very short lived improvement after operation. It was this disadvantage attaching to undercutting that led to the abandonment of this method of isolating a small area of prefrontal cortex (Curran and Partridge 1952). As Meyer and Beck point out their findings do not imply that "the more the frontal lobe is cut the better will be the result but it does mean that the cut must be adequate in order to be effective".

Now it has long been suspected that prefrontal leucotomy and convulsive treatment exert some of their effects through common

neurological channels. The view has sometimes been expressed that convulsive treatment was a mild, temporary leucotomy. It is to be doubted whether the two treatments can be equated to this extent in that although their effects on the psychosis are similar in endogenous depression and some types of schizophrenia, leucotomy is often effective in chronic neuroses, whereas no such success can be claimed for ECT. But the striking changes in sleep rhythm, the menstrual cycle, appetite and body weight and the alterations in autonomic function produced by each indicate that stimulation into activity of diencephalic regulating centres is common to them. Moreover, each form of treatment is non-specific exerting a beneficial influence upon a range of psychiatric disorders so wide that there cannot be any casual factor common to them all. This non-specificity is more marked in the case of leucotomy but it seems likely that both treatments act not on the causes of mental illness directly but either on general homeostatic mechanisms that may be stimulated into activity so as to counteract the pathogenic effects exerted by these causes or by a transient or lasting disruption of physiological processes essential to the perpetuation of mental disorder.

Further suggestive evidence that they have some important factor in common is provided by comparison of the site of action of the two treatments and of the clinical effects they exert. The degree of parallelism that thus emerges lends confirmation to the view that the EEG changes described above are intimately related to the cerebral process that promotes recovery. The EEG changes produced by ECT are frontally preponderant. As they subside completely within some two months of treatment we know also that they are reversible and correspondingly it is a well-known limitation of ECT that the clinical effect is confined to the attack treated and that the chances of recurrence are unaffected. On the other hand, in the case of leucotomy, the anatomical lesion of the frontal lobes or its connections is, of course, permanent and relapse is relatively rare. Since the data cited above also indicate that a quantitative factor operates to decide the quality and duration of remission in electro-convulsive therapy as in prefrontal leucotomy, it would seem reasonable to conclude that a common action on the frontal lobes is the link between the two treatments. In other words, what is brought about by means of a permanent structural lesion in prefrontal leucotomy, may be achieved in the case of ECT by means of the short-lived frontally predominant EEG change it produces. And in that the severance of thalamo-frontal connections is indubitably the cause of the recovery from mental illness that follows it, the frontally predominant delta waves may also be linked in an intimate manner with the changes in the brain promoting recovery in the course of electroconvulsive treatment.

It would seem therefore that temporary or permanent interruption of thalamo-frontal connections tends to be followed by effects on psychotic behaviour patterns that are themselves short-lived or lasting.[1] And the quantitative factor shown in this paper to operate in relation to the slow activity induced by convulsions is likely to issue from the same principle that underlies the decisive influence on prognosis in prefrontal leucotomy exerted by the extent of the thalamo-frontal projection that has been divided (Meyer and Beck 1954).

If the argument pursued here is valid, electroconvulsive therapy as well as leucotomy may owe their effects partly to an interruption of cerebral processes that are physiological in character but have come to serve the needs of pathological processes.

In previous papers (Roth 1951, 1952; Roth and Rosie 1953) attention was drawn to the non-specificity of ECT. It was pointed out that it was effective to some extent in disorders caused by such a wide range of causal agents that its effects were more likely achieved through regulating and defensive mechanisms rather than a direct action on the causes of the mental illnesses as such. Such an influence is, in fact, evident in the changes in sleep rhythm, menstrual cycle, in autonomic function and increased activity of the anterior pituitary, and it was also suggested then that the EEG changes might reflect an increased influence by the diffuse projection system on

[1] This does not of course imply that leucotomy is the better procedure; the likely duration of the effect on the psychosis is not the only consideration in choice of treatment.

the electrical activity of the cortex. The mode of action suggested was one analogous to that of substances such as ACTH and cortisone which are also more or less effective in many disease processes ranging from asthma to rheumatoid arthritis, though clearly do not influence the basic causes of these diseases. But this view is not necessarily correct. For non-specificity of a treatment might alternatively be due to the fact that it interrupts the final common pathway of a variety of diseases or interferes with physiological processes upon which pathological activities have become dependent. An example of this nature from another branch of medicine is the effect of bilateral adrenalectomy in causing regression of carcinoma of the breast or prostate as well as their metastases.

Since pre-frontal leucotomy destroys a part of the brain, and since for the reasons indicated it is likely to exert some of its effects through neurological channels common to those utilized by convulsive treatment, an essential element in these treatments may well be analogous to such procedures. They may owe their efficacy to the fact that the thalamo-frontal system which they each influence comes to play an essential link in the chain of neurological events that perpetuate certain mental disorders. To give any adequate consideration to the physiological character of these events would require more knowledge than is available about the frontal lobe and its connections, and would in any case be beyond the scope of this paper. But it is not difficult to conceive how such integrative functions as have been attributed to the pre-frontal region and its connections in relation to the development of some aspects of personality could serve also to bring about an integration of psychotic with pre-morbid personality patterns. Certain data about pre-frontal leucotomy would appear to demand some such explanation. But these matters will be discussed elsewhere.

The changes in the activities of regulating centres observed during ECT and following pre-frontal leucotomy may thus have an alternative explanation to that which allocates to them an important role in the restoration of a relatively stable pattern of cerebral activities (Roth 1952; Roth and Rosie 1953). Their activity may be merely a compensatory response evoked by the disturbing influence of a destructive lesion in one case (leucotomy) and what must be regarded as a functional interference with extensive but predominantly frontal areas of cortex, in the other (convulsive treatment).[1] It is known in effect that no attempt at reproducing all the vegetative and endocrine changes produced by these procedures has, in fact, the slightest influence upon the psychosis.

But although the data discussed here suggest that the subtle and temporary interference with cortical activity (predominantly in the frontal region) that is likely to be the primary factor in the efficacy of ECT as well as the explanation for its non-specificity, and that the marked vegetative changes are likely to be secondary, it is not possible at the present time to decide in any conclusive way what is the precise relationship between these three crucial and characteristic features of the treatment. When the interrelationship between the negative effects (as evidence the EEG changes, memory impairment and disappearance of psychotic behaviour pattern) the non-specificity and the vegetative changes has been elucidated, we ought to be near to an understanding of the mode of action of convulsive treatment and perhaps pre-frontal leucotomy.

SUMMARY

1. A new technique for evaluating the changes produced in the brain by electroconvulsive therapy is described. It is based on measurements of the run of delta activity that appears following a standard injection of sodium thiopentone within 3-4 hours after a convulsion. This delta activity has a finite duration which never exceeds 300 sec. and the measurement consists of plotting the changing value during courses of ECT of the percentage of time occupied by delta waves during the 300 sec. following their appearance.

In cases of endogenous depression it has been found that this measurement shows a

---

[1] There is some evidence to suggest that the appearance in the EEG of the diffuse, high voltage, rhythmic frontally predominant slow waves to which reference is made here, is secondary to activation of the diffuse projection system (Roth 1951).

closer association with the clinical changes during an ECT series than EEG changes in the ordinary record. The per cent time score shows a progressive increase with successive ECT but reaches a plateau and occasionally shows a decline from the peak in courses of more than nine. The shape of the curve and the peak value reached show a wide range of variation in different individuals for identical courses.

3. This range of variation is of significance for prognosis. Those with peak values of under 40 per cent show significantly higher relapse rates than those with values above this figure, at 3 and at 6 months after the end of treatment. The mean peak value of the slow activity is significantly lower in relapsed cases than in those maintaining stable remissions.

4. It would seem likely that cases of endogenous depression attaining values of 35 per cent or below have not acquired an adequate physiological basis for recovery. On this basis a simple tentative method for applying the observations is suggested.

5. The changes are frontally predominant and it is suggested that the quantitative principle shown to operate in the relationship between prognosis and thiopentone induced slow activity may be identical with that shown (by the relationship between outcome and extent of the lesion in thalamo-cortical fibres) to operate in relation to prefrontal leucotomy. The evidence suggests that the factor held in common by the two forms of treatment is the derangement in function of the thalamo-frontal system, temporary in the case of ECT, permanent in leucotomy.

6. It is this relative inhibition or partial elimination of thalamo-frontal system that may be related to the non-specificity of the two treatments and perhaps the vegetative changes are secondary to the disturbing influence of the convulsions and prolonged dysrhythmia in one case, and the surgical lesion in the other.

REFERENCES

CURRAN, D. and PARTRIDGE, M. Prefrontal Leucotomy. In *Surgical Progress.* London, Butterworth, **1952**, 162-170.

MEYER, A. and BECK, E. *Prefrontal Leucotomy and Related Operations: Anatomical Aspects of Success and Failure.* London, Oliver and Boyd, **1954**, 40 pp.

MORIARTY, J. D. and SIEMENS, J. C. Electroencephalographic study of electric shock therapy. *Arch. Neurol. Psychiat.*, Chicago, **1947**, *57*: 712-718.

ROTH, M. Changes in the EEG under barbiturate anaesthesia produced by electro-convulsive treatment and their significance for the theory of ECT action. *EEG Clin. Neurophysiol.*, **1951**, *3*: 261-280.

ROTH, M. A theory of ECT action and its bearing upon the biological significance of epilepsy. *J. ment. Sci.*, London, **1952**, *98*: 44-59.

ROTH,, M., SHAW, J. and GREEN, J. The effect of ECT on the EEG response to sensory stimulation. Unpublished observations. **1956**.

ROTH, M. and ROSIE, J. M. The use of electroplexy in mental disease with clouding of consciousness. *J. ment. Sci.*, London, **1953**, *99*: 103-111.

Reference: ROTH, M., KAY, D. W. K., SHAW, J. and GREEN, J. Prognosis and Pentothal induced electroencephalographic changes in electro-convulsive treatment. *EEG Clin. Neurophysiol.*, **1957**, *9*: 225-237.

PRINTED IN CANADA

EDITORIAL NOTE

CORRECT TERMINOLOGY

ALEXANDER FORBES, M.D.
The Biological Laboratories, Harvard University, Cambridge, Mass.

Two words, commonly used in neurophysiology, are frequently misused in ways that may cause serious confusion. These words are electrode and volley.

Webster's New American Dictionary (1956) correctly defines "electrode": "either terminal of an electric source, an anode or a cathode". Very frequently in physiological literature, two or more electrodes, mounted together for convenience of manipulation, are called "an electrode" (cf. Burlo 1955). The temptation to do so is especially strong in the case of a concentric pair of electrodes made by inserting an insulated wire inside a hypodermic needle. The apparent unity of the device in no way justifies the misuse of a clearly-defined word. An earlier protest against this abuse (Forbes 1935) has been almost universally forgotten; hence the need to reiterate it.

To call a pair of electrodes a "bipolar electrode" is exactly on a par with calling a pair of gloves a "bimanual glove". A term borrowed from physics with a well-defined meaning should not be used in a different sense through the caprice of the physiologist. To do so is almost certain to cause confusion, especially since it is common practice in some experiments to use a single localizing electrode with a remote diffuse electrode to complete the circuit. The reader seeing the word "electrode" does not know whether the author really means one electrode or two.

The word "volley" has frequently been misused in a way which can cause even more serious confusion. It is defined in the above-named dictionary as "the shooting of many missiles at once". I believe Sherrington first introduced it into physiology to denote the synchronous firing of impulses in all or most of the fibers in a nerve, as is done when a single brief stimulus is applied. It is also applicable to the resulting discharge of impulses in the motor neurones, e.g. in the flexion reflex, in which all neurones discharge simultaneously. The lack of perfect synchronism in such a discharge is analogous to that of a squad of soldiers whose reaction times to the order "fire" differ by a small fraction of a second. In either case the word "volley" is legitimate.

The improper use of the word, frequently found in the literature, is its application to a train of successive discharges from one or more neurones. This phenomenon commonly occurs in the nervous system and is quite different from a volley in the proper sense of the word (cf. Forbes *et al.* 1949, footnote p. 141). The difference is significant and important.

REFERENCES

BURLO, J. M. A multiple electrode for depth recording. *EEG Clin. Neurophysiol.*, **1955**, *7*: 655.

FORBES, A. Electrodes come in pairs. *Science*, **1935**, *81*: 461-462.

FORBES, A., BATTISTA, A. F., CHATFIELD, P. O. and GARCIA, J. P. Refractory phase in cerebral mechanisms. *EEG Clin. Neurophysiol.*, **1949**, *1*: 141-175.

PRINTED IN CANADA

OBSERVATIONS ON THE RESPONSE TO PHOTIC STIMULATION IN ORGANIC CEREBRAL DYSFUNCTION

KENNETH A. KOOI, M.D., H. GERHARD ECKMAN, M.D.
and MADISON H. THOMAS, M.D.

Neurology Service, Veterans Administration Hospital, Fort Douglas Division and the Neurology Section, Department of Psychiatry, University of Utah College of Medicine, Salt Lake City, Utah

(Received for publication: August 6, 1956)

INTRODUCTION

The alteration of the spontaneous rhythms of the brain by rhythmic photic stimulation was first reported by Adrian and Matthews (1934). They noted that the potential waves of the flicker response usually occurred at the same rate as the stimulus. Occasionally, rhythms could be obtained at double or half the rate of the flickering light. Walter and Walter (1949) have emphasized that the response is actually compound at all times, demonstrating multiple harmonic and subharmonic components. Photomyoclonic and photoconvulsive responses have been identified and studied particularly in relation to the epilepsies (Walter, Dovey and Shipton 1946; Walter 1946; Gastaut, Roger and Gastaut 1948; Walter and Walter 1949; Lerique-Koechlin, Nekhorocheff and Le Mansec 1950; Daly and Bickford 1951; Bickford, Sem-Jacobsen, White and Daly 1952; Buchthal and Lennox 1953; Mundy-Castle 1953; Herrlin 1954; Laget and Humbert 1954).

The photic response of patients with organic cerebral lesions has received comparatively little attention. Walter and Walter (1949) cited two cases with unilateral lesions. Using electronic frequency analysis they noted differences in the proportion of fundamental and harmonic components over the two hemispheres. In one case, the response at the fundamental to an 8 c/sec. stimulus was more prominent than a 24 c/sec. harmonic component over the normal hemisphere, whereas on the side of the lesion the proportions were reversed. In a second case, a smaller response was demonstrated on the side of the lesion at fundamental frequencies below 18 c/sec. Weil (1952), however, has described a patient with a unilateral parieto-occipital skull fracture in which the affected areas responded more readily to intermittent flicker than the contralateral homologous regions. Weil and Nosik (1952) found that photic stimulation brought out gross desynchronization of the pattern (''hemispheric activation'') over the affected temporo-occipital areas in three patients with homonymous hemianopsia. In a report of electroencephalographic findings associated with subdural hematoma, Rodin, Bickford and Svien (1953) stated that the photic response was absent or poor in 14 cases, bilaterally equal in 9, better on the normal side or side of the smaller hematoma in 8 and better on the side of the hematoma in 6. Although no consistent lateralization of response was observed they noted a possible relationship between the occurrence of a delta focus and suppression of the photic response. Farbrot (1953) noted similarly, but in patients with cerebro-vascular accidents, that suppression of the photic response may occur at the border of a delta focus to high frequencies (12-27 c/sec.). In addition he observed during the same examination, that slow frequencies of photic stimulation (.8-4 c/sec.) may give high amplitude atypical spike-wave responses arising from the same area that showed suppression to high frequencies. Ostow (1953) noted that the ''quality of driving seems to deteriorate'' when sporadic or serial slow activity is present in the resting electroencephalogram. On the other hand, he found that the quality of driving improves with the

[1] Portions of this study were presented at the meeting of the Central Association of Electroencephalographers, St. Louis, Missouri, Nov. 1954 and at the meeting of the Western Society of Electroencephalography, Phoenix, Arizona, Nov. 1955.

subject's age and concluded that "good quality suggests impaired cerebral functioning such as may accompany aging".

The present study was designed as a general survey of the photic response in a group of patients with heterogeneous organic cerebral disorders in order to assess the relative usefulness of routine photic stimulation in the diagnosis of organic cerebral dysfunction. Characteristics of the photic response, visually analyzed, of 100 patients with organic cerebral damage and 90 control subjects are described. Particular attention is given to the following questions:

1. Are significant differences found between the two groups ?

2. Is a generalization possible about increased or decreased responsiveness in the organic group ?

3. Must visual pathways be involved before the response is altered ?

METHOD

One hundred patients were selected who evidenced cerebral damage at the time of the electroencephalogram from neurological, psychological, arteriographic or pneumographic examination, operative or autopsy findings. In most cases evidence of cerebral involvement was confirmed by more than one investigative technique. The clinical record of each patient was reviewed and sex, age, diagnosis, chronicity of illness, lateralization of lesion, presence of convulsions, ocular findings, visual field defects, spinal fluid pressure, clouding of sensorium, results of skull films, air studies and arteriograms, anticonvulsant and other pertinent medications, psychological test data and operative and post-mortem findings were tabulated. Ventricular dilatation was required to be of moderate or greater degree or definitely asymmetrical before being considered confirmatory evidence. In 21 patients mental symptoms were the only evidence of cerebral dysfunction. These patients had received diagnoses of chronic brain syndrome and all showed moderate to severe impairment on psychological testing. There were 98 males and 2 females ranging in age from 22 to 88 years with a median age of 53. The diagnostic distribution of the patient group is shown in table I. It should be noted that the electroencephalograms were obtained only post-operatively in some patients. In all cases, however, signs of brain damage were present at the time of the electroencephalographic tracing.

The control group consisted of 90 volunteers who were doctors, nurses, aides and students. In no case was there a history of neurologic disorder or a family history of epilepsy. This group included 77 males and 13 females ranging in age from 20 to 60 years with a median age of 26.

TABLE I

CLASSIFICATION OF PATIENTS

Diagnostic Category	*Number of Patients*
Cerebrovascular accident	27
Brain tumor	12
Aneurysm	3
Cerebral trauma	11
Infectious process	7
Chronic brain syndrome	31
Subdural hematoma	4
Epidural hematoma	1
Miscellaneous	4
Total	100

The electroencephalograms were taken with a Grass Model III D electroencephalograph. In the control series standard frontal, central, occipital, and temporal scalp derivations and ear lobe grounds were used. Both scalp-scalp and scalp-ear runs were included. In the clinical group anterior temporal and vertex leads also were used in all routine electroencephalograms. Fifty-eight of the patients received a more extensive localizing examination with additional lower premotor, lateral parietal and posterior temporal leads. In the control group, 86 per cent of the records were considered normal or borderline (6 cases) and 14 per cent abnormal compared with 12 per cent (3 borderline) and 88 per cent respectively in the organic group.

The response to photic stimulation for purposes of group comparison was always estimated from the occipital derivations paired with the combined ears. However, asymmetries were frequently verified by simultaneously recording with other posterior quadrant leads. The occipital leads were carefully placed 8 cm. posterior to the central leads which were centered 4 cm. from the midline on the interaural plane.

The photic stimulation followed a standard procedure in each case. Samples of the response to 20 different frequencies — 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, 26, and 30 c/sec. — and to variable stimulation were obtained. The photic stimulus was presented for 20 sec. with 20 sec. between presentations. During the variable stimulation the rate was continuously varied. This was initiated at 3 c/sec., increased to 20 c/sec., decreased to 10 c/sec. and then rapidly rotated between 10 and 15 c/sec. The photic stimulation was provided by a

Grass Model PS-1 photo-stimulator which gives a blue-white flash of 10 microseconds duration. At the constant intermediate setting that was used throughout the study the peak beam intensity was calculated to be approximately 375,000 candle power. The flash lamp was placed 15 cm. from the eyes and was carefully centered in relation to the level of the eyes and angle of incidence of light rays. The examinations were carried out in a dimly lit room. The subjects' eyes were closed throughout the procedure.

The response to each frequency of photic stimulation was evaluated over each hemisphere in the following fashion. The response at the fundamental frequency was estimated semi-quantitatively with "0" indicating no detectable response, "1" indicating a response identified during less than 10 seconds of the stimulus period and "2" indicating a response identified during more than 10 seconds of the stimulus period. Responses at harmonic or subharmonic frequencies were noted as present or absent. No further subdivision of these components was attempted. Photomyoclonic and photoconvulsive responses were noted as present or absent. An asymmetry was said to exist if a 50 per cent difference in amplitude or incidence of the response between the homologous occipital derivations occurred. Special features of the response were also recorded.

The EEG records were scored without knowledge of the clinical data. Correlations were set up between the various clinical and electroencephalographic variables.

The greatest error in the judgment of the response to photic stimulation would be expected when the frequencies of stimulation were approximately those of spontaneous rhythms. This error was minimized by observation of the form and areal distribution of the response in addition to careful frequency determinations.

RESULTS

The normal response to photic stimulation. All 90 control subjects responded at the fundamental to one or more frequencies of photic stimulation. The response was usually readily visible at many frequencies. Harmonics of the stimulus frequency were common (87 per cent). Subharmonics were noted in 36 subjects (40 per cent). In some instances the response continued unchanged throughout the 20 sec. of stimulation but frequently it was seen to vary in amplitude and form from second to second. It was usual at high frequencies (18 c/sec. and above) for the response to be evident only during the first few seconds of the stimulation period.

The response could be recorded from wide areas over posterior head regions. It was commonly seen in central leads, and differences in the frequency characteristics were noted between occipital and central responses. Central responses at the fundamental were observed that were of higher amplitude than those occurring at the same instant posteriorly, particularly at stimulus frequencies of 6, 7 and 8 c/sec.

The relative group responsiveness at the 19 stimulus frequencies from 3 to 30 c/sec. is seen in figure 1. The estimate of group responsiveness was derived from averaging the response scores at each frequency for each subject. A response at the fundamental was observed more frequently and was likely to be more persistent to those flash frequencies from 9 to 22 c/sec. The controls were divided

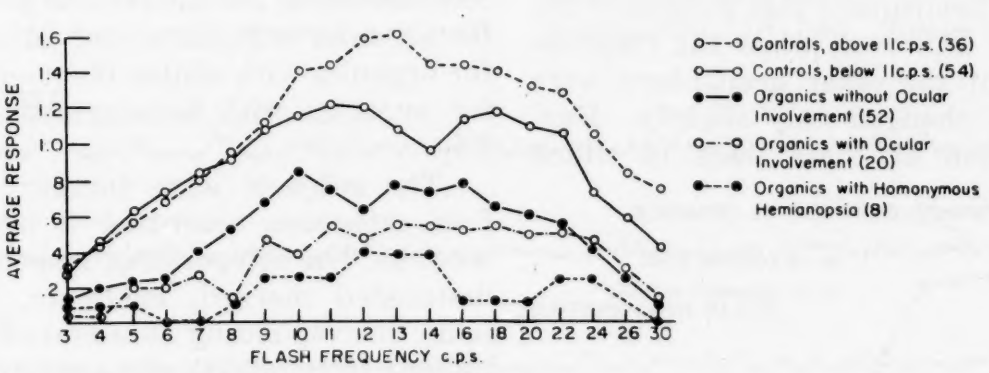


Fig. 1

Average response at frequencies from 3 to 30 c/sec. Controls are divided into those with dominant rhythms above and those below 11 c/sec. Details of ocular involvement in text. Response in the patients with homonymous hemianopsia is that over the hemisphere opposite the field defect.

into two sub-groups, those with dominant frequencies above 11 c/sec. and those below. Subjects with basic patterns faster than 11 c/sec. tended to show a greater responsiveness in the fast and perhaps alpha ranges. A similar finding has been noted by Mundy-Castle (1953).

The frequencies at which harmonic and subharmonic responses were most easily detected are shown in figures 2 and 3.

Comparison of responsiveness between control and organic groups. An attempt was made to compare the relative responsiveness at each frequency between the 90 control subjects and 52 patients without evidence of ocular damage or homonymous hemianopsia. Figure 1 presents the observed differences for the response at the fundamental. The organic group showed a reduction of responsiveness over the entire frequency range when compared with either of the control subgroups. The curve was derived using the response over the hemisphere that presented the lesser response. However, when the response characteristics of the other hemisphere were used, the curve changed only slightly. Furthermore, deletion of those cases in which

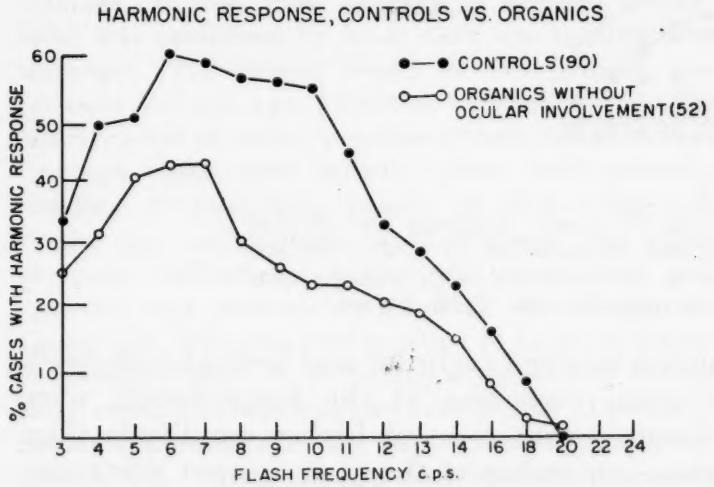


Fig. 2

there was prominent delta activity in the occipital leads did not alter the curve. In a group of 27 cases with ocular damage including unilateral or bilateral optic atrophy, papilledema, macular degeneration, chorioretinitis, retinal artery thrombosis and cataracts, the response at each frequency was slightly less than in the organic group without ocular lesions. Figures 2 and 3 present a comparison of the occurrence of harmonic and subharmonic responses. Organically damaged subjects demonstrated fewer detectable harmonic responses. The findings for subharmonics were equivocal.

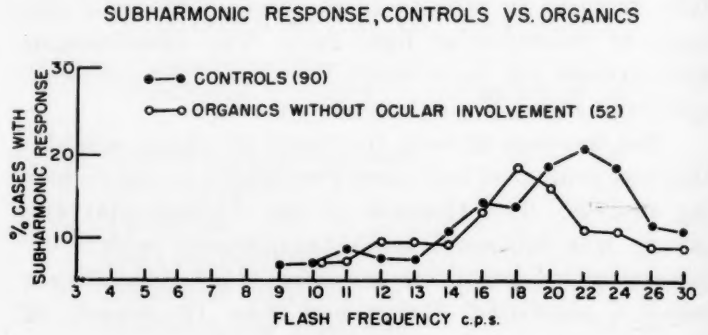

SUBHARMONIC RESPONSE, CONTROLS VS. ORGANICS
% CASES WITH SUBHARMONIC RESPONSE
CONTROLS (90)
ORGANICS WITHOUT OCULAR INVOLVEMENT (52)
30
20
10
3 4 5 6 7 8 9 10 11 12 13 14 16 18 20 22 24 26 30
FLASH FREQUENCY c.p.s.

Fig. 3

A judgement of over-all responsiveness to photic stimulation was determined for each subject by adding the numerical estimate of the response at the fundamental for each frequency from 3 to 30 c/sec. Average over-all responsiveness for the control group was 17.0, for organics without ocular involvement, 8.8, for organics with ocular involvement, 5.4, and for organics with homonymous hemianopsia, 3.4.

The subjects were further grouped into four categories according to over-all responsiveness. The categories of responsiveness were designated marked, moderate, minimal and none, corresponding to scores of 21 to 30, 11 to 20, 1 to 10, and 0, respectively. The results are indicated in table II. There was a general trend to lesser responsiveness in the organic groups. Absence of detectable response occurred only in the patient groups. Marked over-all responsiveness was observed appreciably less frequently in the organic group and no single organic case with an active response was found whose score could not be duplicated by one or more subjects in the control group.

Lateralization of the photic response. Lateralized responses were of two types, those showing a difference in amplitude or incidence (50 per cent or more) of the repetitive response to flash frequencies of 4 to 30 c/sec. (figs. 4 and 5) and those showing an amplitude difference (50 per cent) of single responses to 1 c/sec. and rarely 3 c/sec. stimuli (fig. 6). Subjects with shifting asym-

TABLE II

CATEGORIES OF RESPONSIVENESS IN CONTROL AND ORGANIC GROUPS

Photic Response	*Control Group*		*Organic Group without Ocular Involvement*		*Organic Group with Ocular Involvement*		*Organic Group with Homonymous Hemianopsia*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Marked	36	40.0	4	7.7	1	5.0	0	0.0
Moderate	43	47.8	19	36.6	5	25.0	1	12.5
Minimal	11	12.2	23	44.2	6	30.0	3	37.5
None	0	0.0	6	11.5	8	40.0	4	50.0
Totals	90	100.0	52	100.0	20	100.0	8	100.0

metrical responses or bilateral responses characterized by differences in fundamental, harmonic or subharmonic content were not considered in the tabulation. There were 39 cases with clinical evidence of direct involvement of only one hemisphere, with or without visual impairment. This group included patients with cerebro-vascular accidents, brain tumors and focal infectious processes. Of these 39, 18 (46 per cent) showed a significant difference in the photic response over the two hemispheres. Of the remaining 61 cases with known or possible bilateral damage, 14 (23 per cent) showed such a lateralization. Five (6 per cent) of 90 controls showed a similar finding. The relationship between clinical and electroencephalographic lateralization can be restated this way. Of the 32 patients with an asymmetrical response to photic stimulation, 18 had clinically unilateral le-

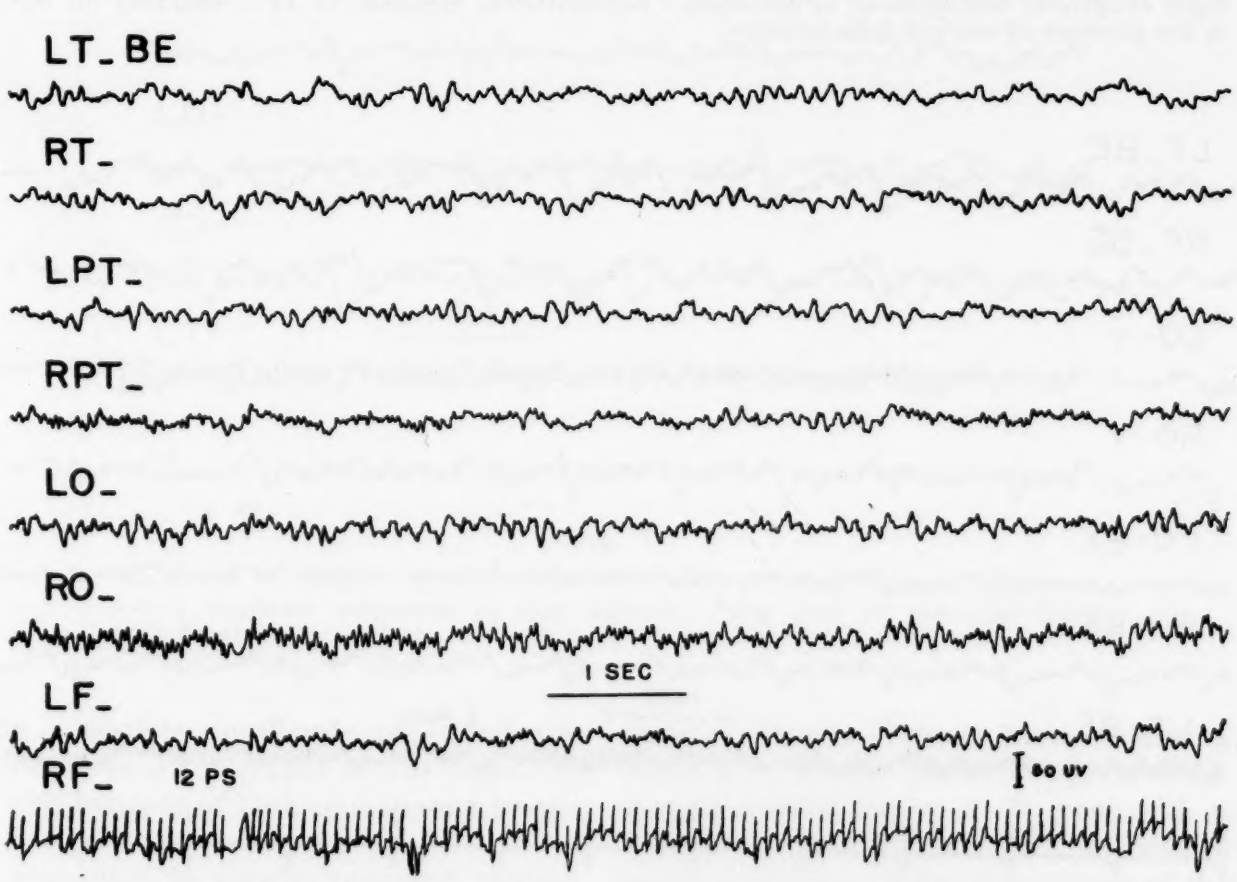


Fig. 4

Male, age 60, cerebrovascular accident 2½ years prior to EEG examination. Right hemiparesis, mixed aphasia. Note lack of response on left. In this and subsequent figures scalp leads are designated F-frontal, LP-lateral parietal, M-motor, O-occipital, PT-posterior temporal, T-temporal, reference leads, BE-both ears, V-vertex, L-left, R-right.

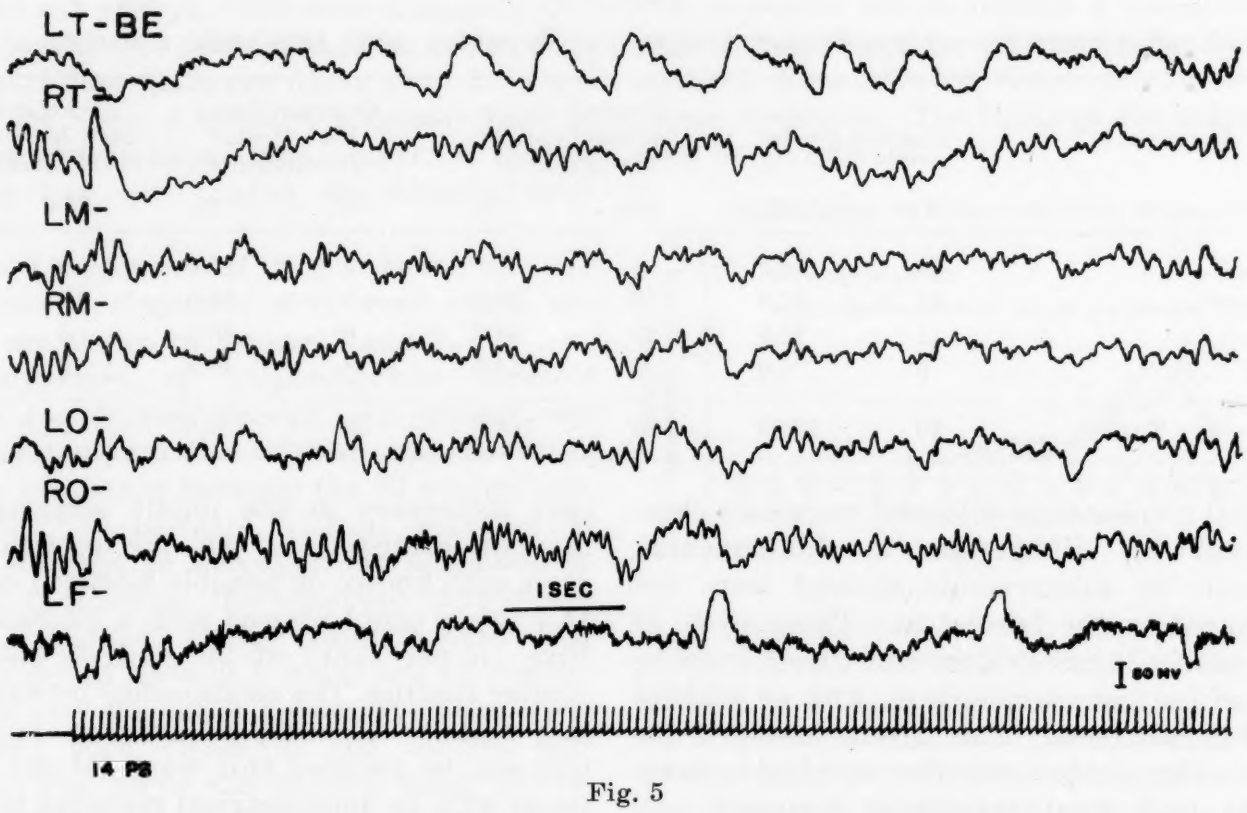


Fig. 5

Male, age 23, cerebrovascular accident 3 weeks prior to EEG examination. Right hemiparesis, right congruous homonymous hemianopsia. Asymmetrical response to 14 c/sec., less on left, in the presence of marked delta activity.

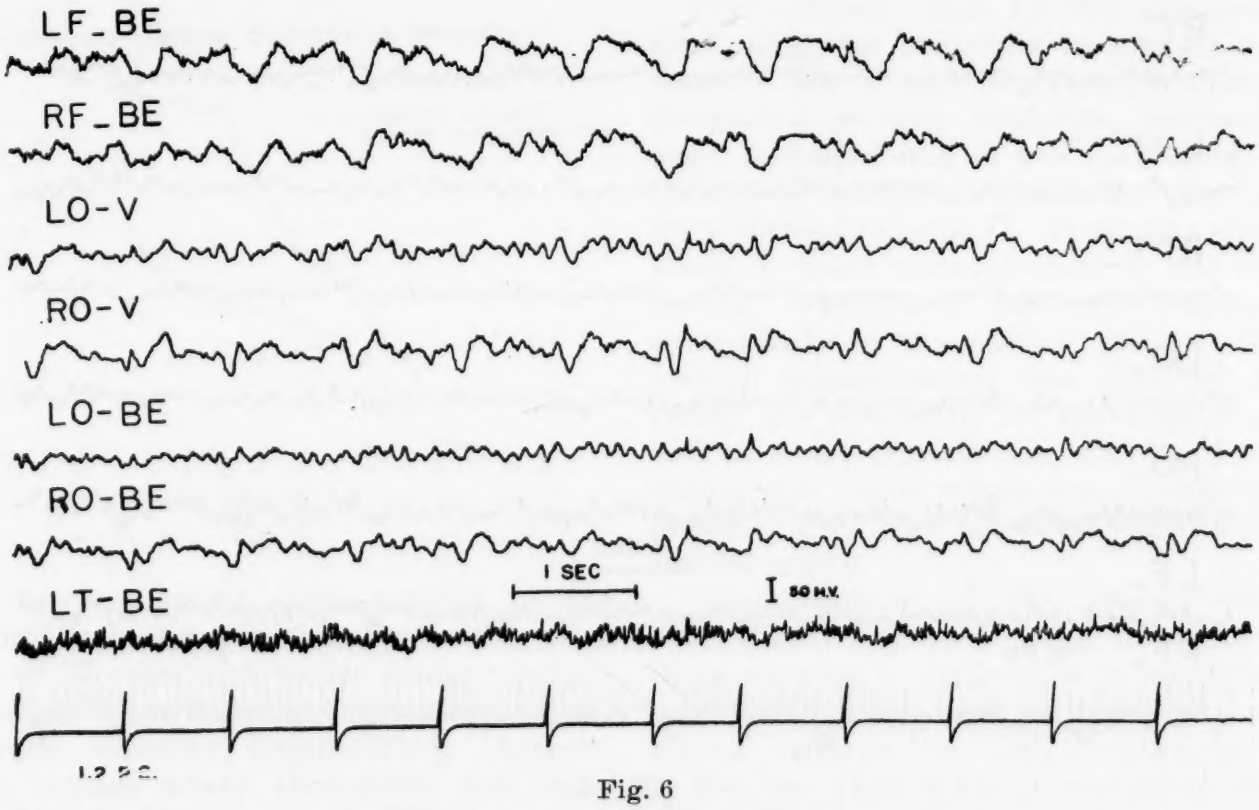


Fig. 6

Male, age 61, cerebrovascular accident 17 months prior to EEG examination. L. hemiplegia, no hemianopsia. Broad triphasic responses to slow stimuli on lesion side.

sions. The other 14 cases are of interest because of the possibility of hemispheric differences in the location and extent of cerebral damage. The diagnoses in these 14 cases were post-traumatic encephalopathy (7), subdural hematoma (2), multiple cerebro-vascular accidents (1), encephalitis (1), hypertensive encephalopathy (1), multiple sclerosis (1), and subarachnoid hemorrhage (1).

The asymmetry of the response in the 18 lateralized cases was characterized by lesser response on the side of the lesion to frequencies in the 4 to 30 c/sec. range in 15 cases; by a higher amplitude of broad triphasic responses on the side of the lesion in 2 cases; and because of both phenomena in one case.

The responses to slowly repeated stimuli were of special interest. These responses, occurring to 1 c/sec. and infrequently to 3 c/sec. flash rates, were characteristically broad, triphasic formations of 50-80 μV. Responses of this type were not seen in the control group. As noted above, they occurred three times in patients with unilateral lesions, either appearing only on the side of the lesion or with higher amplitude on that side (fig. 6). Four additional patients whose lesions were questionably or non-lateralized showed this type of response. In two it was bilaterally equal and in two asymmetrical. It should be noted that other cases have been studied in which this type of response was not initially apparent with routine testing but could be elicited by increasing the flash intensity. Figure 7 shows these occurring symmetrically in the posterior leads with some spread anteriorly in a 74 year old patient with paralysis agitans and a marked organic brain syndrome. When formations of this type were present, responses to faster stimulus frequencies were absent or minimal. None of these patients had seizures.

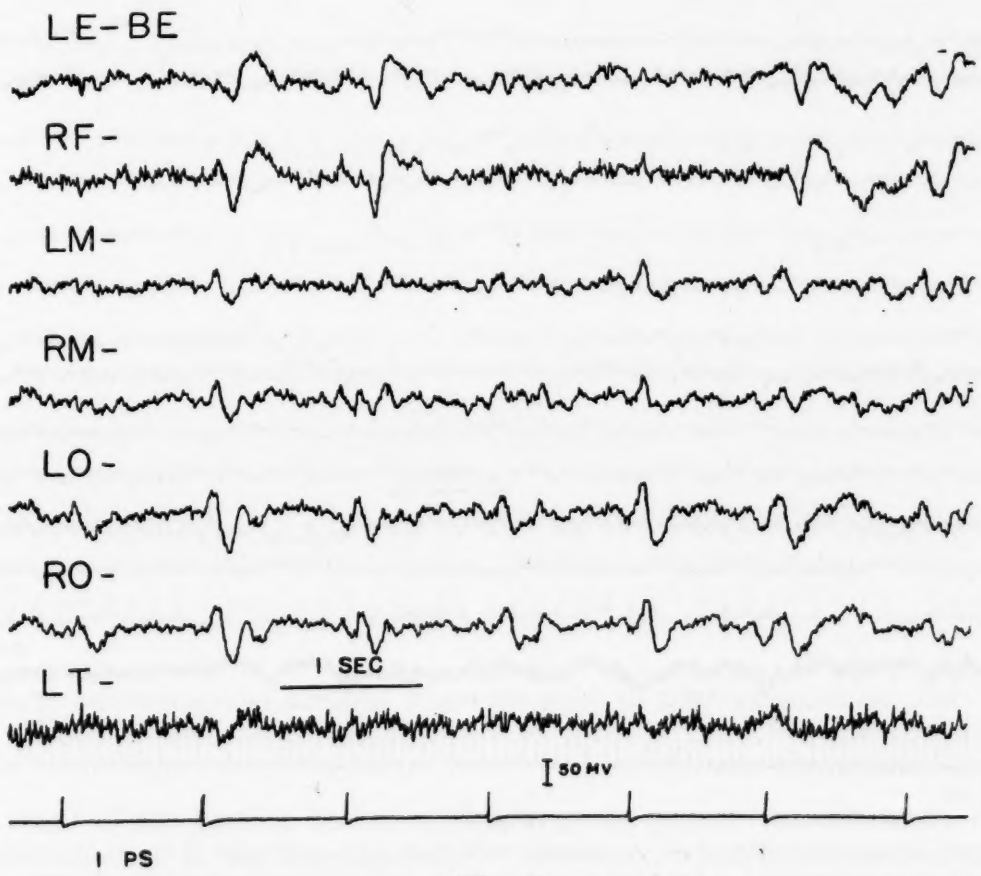


Fig. 7

Male, age 74, marked organic brain syndrome, paralysis agitans. Bilateral broad triphasic responses to slow stimuli. Note lack of correspondence with frontal eye artifacts.

Asymmetries in response were seen over

the entire range of frequencies, roughly paralleling the occurrence of response at each frequency.

Photic response in homonymous hemianopsia. A small group of 9 patients demonstrated homonymous hemianopsias. One of these also had optic atrophy and had no detectable response to photic stimulation. The average response of the remaining 8 for each frequency on the side of the lesion is shown in figure 1. The average response was less at each frequency than in any of the other groups. Five showed no response, 2, minimal, and 1, good, over the hemisphere contralateral to the hemianopsia. The response was seen more clearly over the other hemisphere in 5 of the cases. Two of the cases showed no or minimal response over either side. In the other case, the response was well marked and of greater amplitude over the hemisphere contralateral to the hemianopsia (fig. 8). This last case is of interest because of its lack of similarity to the other 7. These 7 were noted to have hemiplegia with or without aphasia. Congruous field defects were present in 6 with perimeter testing. Perimeter fields were not obtainable in the other case because the patient was not cooperative. However, a hemianopic defect was repeatedly demonstrable by confrontation. In contrast, the patient with the unexpectedly strong response was found to have incongruous field changes, thalamic sensory changes and extrapyramidal involuntary movements. There is the possibility that this last patient might have had optic tract involvement as opposed to the more usual involvement of the optic radiations.

Of those cases without ocular damage, an asymmetry of the photic response was observed in 6 of 8 patients with homonymous hemianopsia and 7 of 17 patients with lateralized lesions without demonstrable field defects. All of the patients with homonymous hemianopsia with a lesser response over the side of the lesion also showed slow formations in the resting record on that side except for one case (fig. 9).

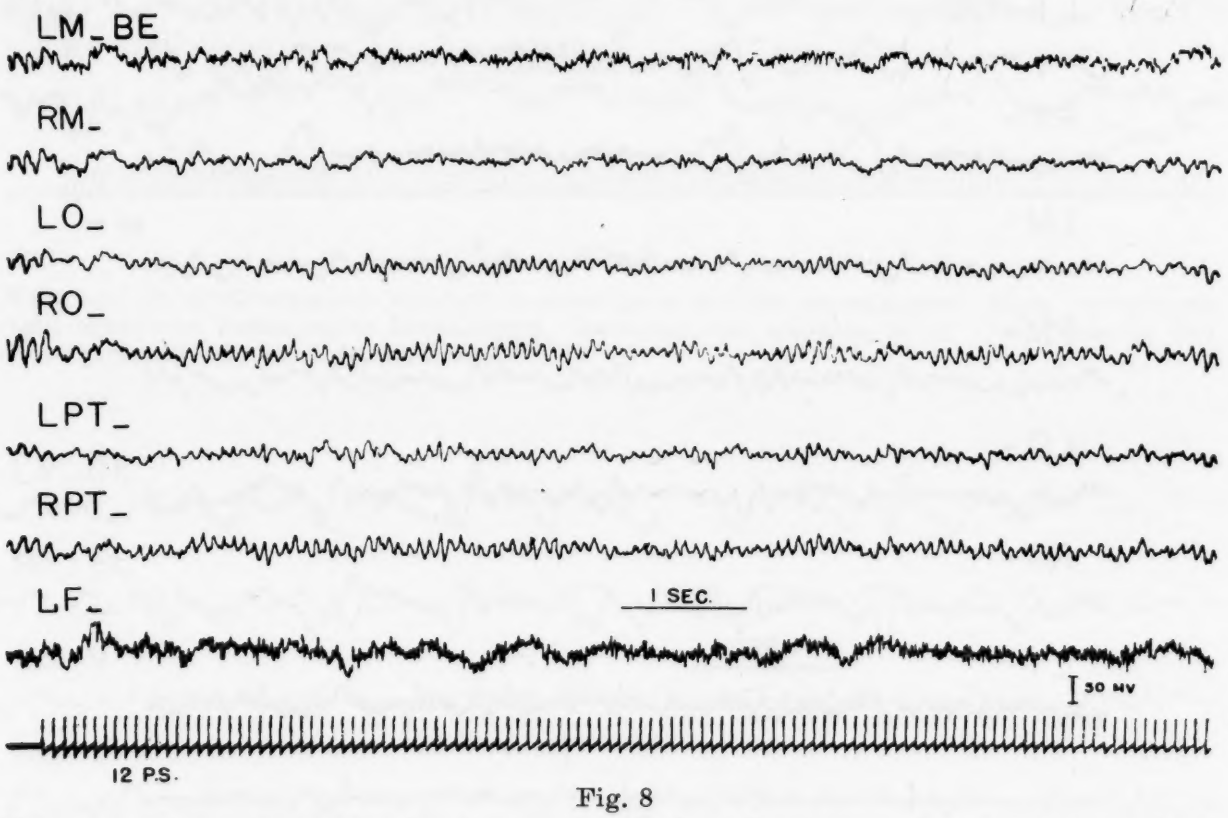


Fig. 8

Male, age 42, encephalopathy due to remote infection. Incongruous left homonymous hemianopsia, left extrapyramidal involuntary movements, left thalamic sensory change. Atypical response in patients with homonymous hemianopsia in that the response is equal or greater on the side opposite the field defect.

Photomyoclonic and photoconvulsive responses. Four of the organic group demonstrated photomyoclonic responses. None of

these had a history of convulsions although 29 of the patients gave such a history. Two of the patients with photomyoclonic responses were diagnosed cerebral thrombosis, 2, general paresis. Photomyoclonic responses were not seen in the control group. Photoconvulsive responses did not occur in either group.

Photic responses in relation to the resting EEG. A tabulation was made of the 52 cases without ocular damage or homonymous hemianopsia correlating the basic frequency (non-involved side) of the resting record with average over-all response at the fundamental. Five patients with low voltage fast records were omitted from the tabulation. A possible trend was noted in that of the 24 patients with basic frequencies slower than 9 c/sec., 15 (62.5 per cent) showed less than average over-all responsiveness, whereas of the 23 patients with frequencies higher than 9 c/sec., 9, (39.1 per cent) showed less than average response. That an active response to photic stimulation may occur in the presence of a slow basic pattern is shown by 3 cases with dominant 7-8 c/sec. patterns whose over-all responsiveness exceeded the average for the normal control group. A correlation of basic frequency with harmonic responsiveness revealed no apparent trend.

The presence of moderate and marked unilateral delta activity was usually associated with reduction of response as compared with the contralateral hemisphere. The response did not differ significantly in those patients with small amounts of unilateral or shifting delta activity and those without it. The presence of delta activity alone did not account for the reduced responsiveness in the organic group inasmuch as average responsiveness at the fundamental was 10.5 for patients without delta activity and, as previously noted, 17.0 for controls.

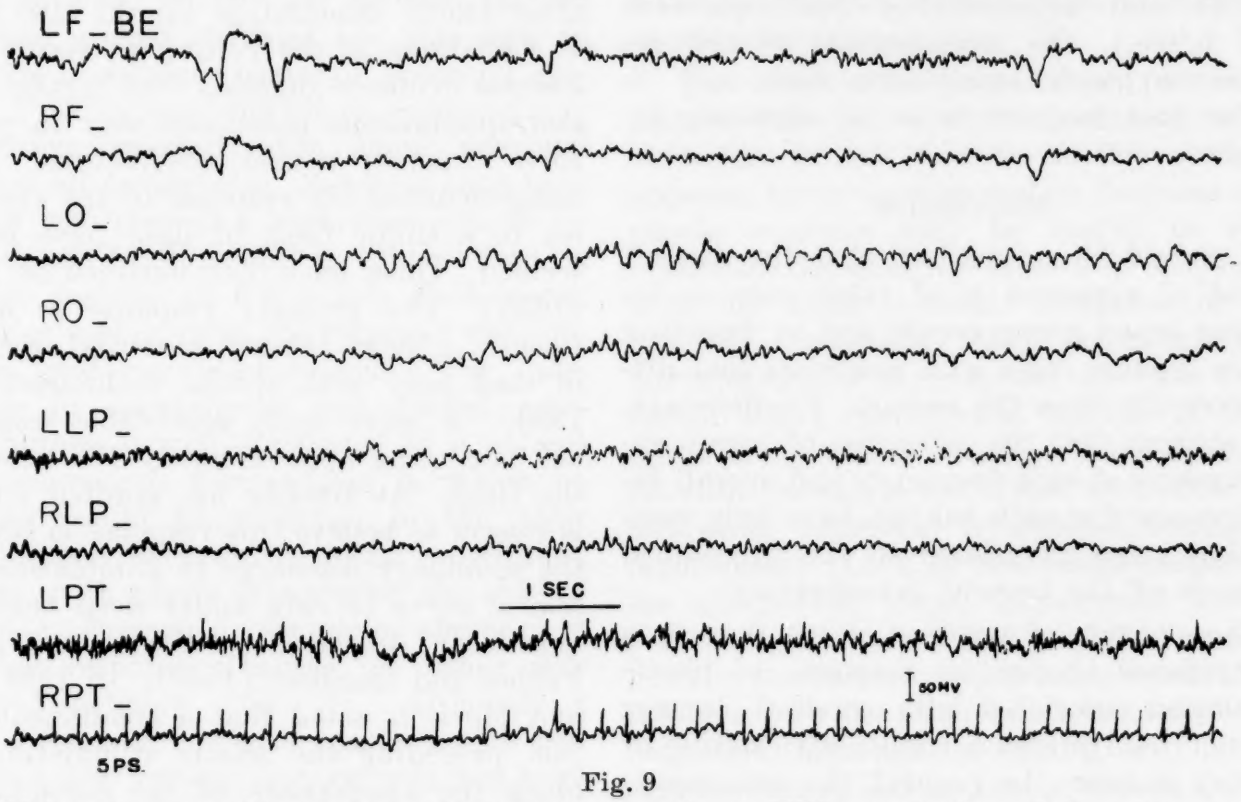


Fig. 9

Male, age 68, cerebrovascular accident 2 months prior to EEG examination. Left congruous homonymous hemianopsia. Response decreased in right occipital and right lateral parietal leads.

The EEG records of the 32 patients with asymmetrical responses to photic stimulation were reviewed to determine whether there were corresponding asymmetries of the basic pattern. Nineteen showed a 50 per cent difference in alpha or subalpha amplitude or incidence with the asymmetry paralleling that to photic stimulation. Eleven showed a symmetrical basic pattern. In 2 cases, alpha activity was more evident on the side opposite the more pronounced photic response. Of the 5 controls that revealed an asymmetry of

response, only one demonstrated a similar asymmetry of the basic pattern. One of the organic cases with reversed asymmetry of the dominant pattern and photic response had a clearly lateralized lesion (brain tumor). The response to photic stimulation was characteristically reduced over the side of the lesion even though the background pattern, which was in the normal alpha range, was of higher amplitude than over the non-involved hemisphere. In many cases, both with symmetrical and asymmetrical basic patterns (7-13 c/sec.), the asymmetries of the responses to photic stimulation were only to slow or fast frequencies or in harmonic responses.

DISCUSSION

It should be emphasized that the present method of approach is of value only in indicating broad group trends and in detecting certain organic cases with responses that differ markedly from the normal. Furthermore, it is obvious that the estimates of group responsiveness at each frequency and overall responsiveness for each subject have only comparative value as related to the procedural constants of the present investigation.

The question of whether or not there is a undirectional change in response to photic stimulation associated with cerebral damage does not resolve into a simple affirmative or negative answer. In general, the response is reduced. This is demonstrated not only by the observed differences between the normal and patient groups but also by the frequent finding of lesser responsiveness of the involved hemisphere when unilateral cerebral damage is present. However, the frequency of the stimulus must be considered inasmuch as broad high amplitude responses may occur to slow stimuli (1-3 c/sec.) in the face of a reduced response to higher frequencies. These observations parallel those of Farbrot (1953).

Our findings do not support the concept that increased responsiveness to photic stimulation occurs in association with mental deterioration unless it is limited to a consideration of the distorted high amplitude responses to slow stimuli. On the contrary, an active response to a broad range of frequencies characterizes the normal effect of rhythmic visual stimulation.

The clinical usefulness of photic stimulation for the diagnosis of organic cerebral dysfunction depends in part upon whether the response is a different order of cerebral activity than the spontaneous rhythms. It is clear that if the photic response is merely a rearrangement of events occurring spontaneously which are evident in the resting electroencephalogram that the variations observed after photic stimulation should also be seen as variations in the resting pattern. Experimental evidence suggests that certain evoked and spontaneous potentials may in part involve common neural mechanisms. Several components of the response of the visual cortex to a single flash of light have been described. These have been outlined by Brazier (1953). The primary response to a single flash is a short latency potential, recordable in man only with special techniques (Cobb 1950). A more easily recordable response is one beginning approximately 100 msec. after the flash. As Brazier has pointed out there is reason to believe this response is similar to the secondary discharge to stimulation of the sciatic nerve in cats under deep barbiturate anesthesia, described by Derbyshire, Rempel, Forbes and Lambert (1936). In 1939 Forbes and Morison noted that a spontaneous wave just preceding the sciatic stimulation could block the appearance of the secondary discharge and inferred that both may involve the same mechanism. Bishop and Clare (1952) have reviewed the studies of the evoked response in the visual system which also led them to the inference of a common mechanism between the after-discharge of the evoked response and spontaneous alpha activity. Identification of the repetitive photic response as involving a common neural mechanism with alpha activity is supported clinically by the instances in which the alpha rhythm appears to be completely supplanted by the new photically evoked rhythm.

On the other hand, dissimilarities in the areal distribution of the spontaneous rhythms and the repetitive photic response appear to indicate some independence of the two systems. Walter and Walter (1949) noted that

the same cortical areas were not involved in the photic response and the alpha rhythm. Rodin, Bickford and Svien (1953) in a study of electroencephalographic findings associated with subdural hematoma noted that an asymmetry of alpha activity between the two hemispheres did not always correspond with the asymmetry of the photic response. Our findings also indicate that an asymmetry of the response to photic stimulation frequently does not reflect a similar asymmetry of the resting pattern. Differences between spontaneous and evoked rhythms are also seen in variations in anterior-posterior potential gradients. Furthermore, the photic response may not involve precisely the same neuronal groups at all frequencies. Subjects have been observed who showed a higher amplitude response at the fundamental in central than in posterior regions at 6-8 c/sec. flash rates, whereas at higher rates the response was confined to posterior head regions. The independence of spontaneous and evoked repetitive rhythms is well illustrated by a patient with homonymous hemianopsia in which no difference could be observed in the basic alpha pattern between posterior quadrants. However, with photic stimulation the side of the lesion showed a complete absence of detectable response whereas the other side responded actively (fig. 9). Although a tendency for greater photic response with fast alpha and low voltage fast records has been noted, this is by no means constant and unusually strong responses may occur in normal subjects with high amplitude slow alpha resting patterns. Ulett *et al.* (1953) have emphasized this "latent tendency" to respond. Active responses were also seen in our organic group in several patients with 7-8/sec. dominant frequencies. Thus it is clear that the photic response reveals aspects of neural function not apparent from the resting tracing.

Our evidence suggests that diminution of the response to photic stimulation is likely to occur when visual pathways are involved but that this is not a necessary condition for decreased response (table II). The lack of response on the side of the lesion in patients with homonymous hemianopsia is not unexpected. A lesion of the optic pathways resulting in visual loss should block impulses which would normally arrive at the visual cortex. However, unexplicably, an active response was found in one patient over the hemisphere opposite an incongruous field defect. The significance of this lack of relationship is not clear but one obviously wonders what part associated activity within visual association areas or the reticular activating system may play. Activity in structures not included in the primary visual pathway has been reported (Gerard, Marshall and Saul 1936; Ingvar and Hunter 1955) to occur with photic stimulation.

The information gained from photic stimulation was not used for assessing relative normality of the records in this study. It appears, however, that certain features of the photic response may be useful in record evaluation particularly if used in conjunction with the usual criteria. Evidence of hemispheric abnormality may be indicated by lateralization of the response when the resting record shows symmetrical activity in homologous areas. More usually, lateralization of the response can be correlated with other signs indicating unilateral or unequal hemispheric involvement. Lack of detectable response in the absence of visual impairment and the presence of certain broad triphasic responses leads to the suspicion of organic cerebral dysfunction. On the other hand, photomyoclonic responses, although occurring only in the organic group, did so rarely and in patients without a history of convulsive disorders. Thus no clue is gained as to their possible significance in the framework of the present investigation.

CONCLUSIONS

1. A comparison between a group of 90 control subject and 100 organically brain-damaged patients showed significant differences in response to intermittent photic stimulation.

2. Responsiveness was reduced (4 to 30 c/sec.) in the organic group without visual impairment. A further decrease in responsiveness was observed in the group with both brain and ocular damage. The greatest reduction was noted in a small group of patients with homonymous hemianopsia.

3. Unilateral hemispheric damage with or without a visual field defect was commonly associated with asymmetry of the photic response, the lesser response (4 to 30 c/sec.) in the present series, always being on the side of the lesion.

4. Characteristic broad triphasic responses to slowly repeated stimuli were seen only in the organically damaged group.

5. Photomyoclonic responses were seen infrequently in the organic group and were not observed in the control group. They were not found to be associated with a history of convulsive disorder.

The authors wish to express their appreciation to Doctor H. Birnet Hovey for the detailed review of the psychological test protocols and to Miss Ruth Rowe for excellent technical assistance.

REFERENCES

ADRIAN, E. D. and MATTHEWS, B. H. C. The Berger rhythm; potential changes from the occipital lobes in man. *Brain*, **1934**, *57*: 355-384.

BICKFORD, R. G., SEM-JACOBSEN, C. W., WHITE, P. T. and DALY, D. Some observations on the mechanism of photic and photometrazol activation. *EEG Clin. Neurophysiol.*, **1952**, *4*: 275-282.

BISHOP, G. H. and CLARE, M. H. Relations between specifically evoked and "spontaneous" activity of optic cortex. *EEG Clin. Neurophysiol.*, **1952**, *4*: 321-330.

BRAZIER, M. A. B. A review of physiological mechanisms of the visual system in relation to activating techniques in electroencephalography. *Third Inter. Cong. EEG Clin. Neurophysiol.*, Suppl. No. *4*. **1953**, 93-107.

BUCHTHAL, F. and LENNOX, M. The EEG effect of Metrazol and photic stimulation in 682 normal subjects. *EEG Clin. Neurophysiol.*, **1953**, *5*: 545-558.

COBB, W. A. On the form and latency of the human cortical response to illumination. *EEG Clin. Neurophysiol.*, **1950**, *2*: 104.

DALY, D. and BICKFORD, R. G. Electroencephalographic studies of identical twins with photoepilepsy. *EEG Clin. Neurophysiol.*, **1951**, **3**: 245-249.

DERBYSHIRE, A. V., REMPEL, B., FORBES, A. and LAMBERT, E. F. The effects of anesthetics on action potentials in the cerebral cortex in the cat. *Amer. J. Physiol.*, **1936**, *116*: 577-596.

FARBROT, O. Renseignements apportés par la stimulation lumineuse intermittente à l'étude électroencéphalographique des accidents vasculaires cérébraux. *Acta psychiat. neurol. scandinav.*, **1953**, *28*: 275-286.

FORBES, A. and MORISON, B. R. Cortical response to sensory stimulation under deep barbiturate narcosis. *J. Neurophysiol.*, **1939**, *2*: 112-129.

GASTAUT, H., ROGER, J. et GASTAUT, Y. Les formes expérimentales de l'épilepsie humaine: L'épilepsie induite par la stimulation lumineuse intermittente rhythmée ou "épilepsie photogénique". *Rev. Neurol.*, **1948**, *80*: 161-183.

GERARD, R. W., MARSHALL, W. H. and SAUL, L. J. Electrical activity of the cat's brain. *Arch. Neurol. Psychiat.*, Chicago, **1936**, *36*: 675-738.

HERRLIN, K. M. EEG with photic stimulation: A study of children with manifest or suspected epilepsy. *EEG Clin. Neurophysiol.*, **1954**, *6*: 573-589.

INGVAR, D. H. and HUNTER, J. Influence of visual cortex on light impulses in the brain stem of the unanesthetized cat. *Acta physiol. scand.*, **1955**, *33*: 194-218.

LAGET, P. et HUMBERT, R. Facteurs influençant la réponse électroencéphalographique à la photostimulation chez l'enfant. *EEG Clin. Neurophysiol.*, **1954**, *6*: 591-597.

LERIQUE-KOECHLIN, A., NEKHOROCHEFF, I. et LE MANSEC, M. Valeur diagnostique de la stimulation lumineuse intermittente chez l'enfant. *Rev. Neurol.*, **1950**, *82*: 575-577.

MONNIER, M. Retinal, cortical and motor responses to photic stimulation in man. *J. Neurophysiol.*, **1952**, *15*: 469-486.

MUNDY-CASTLE, A. C. The clinical significance of photic stimulation. *EEG Clin. Neurophysiol.*, **1953**, *5*: 187-202.

MUNDY-CASTLE, A. C. An analysis of central responses to photic stimulation in normal adults. *EEG Clin. Neurophysiol.*, **1953**, *5*: 1-22.

OSTOW, M. Flickered light as a provocative test in electroencephalography. *J. nerv. ment. Dis.*, **1953**, *117*: 429-444.

RODIN, E. A., BICKFORD, R. G. and SVIEN, H. J. Electroencephalographic findings associated with subdural hematoma. *Arch. Neurol. Psychiat.*, Chicago, **1953**, *69*: 743-755.

ULETT, G. A., GLESER, G., WINOKUR, G. and LAWLER, A. The EEG and reaction to photic stimulation as an index of anxiety-proneness. *EEG Clin. Neurophysiol.*, **1953**, *5*: 23-32.

WALTER, W. GREY. Analytical means of studying the nature and origin of epileptic disturbance. *Res. Publ. Ass. nerv. ment. Dis.*, **1946**, *26*: 237-251.

WALTER, W. GREY, DOVEY, V. J. and SHIPTON, H. W. Analysis of the electrical response of the human cortex to photic stimulation. *Nature*, **1946**, *158*: 540-541.

WALTER, W. GREY and DOVEY, V. J. Etude analytique des rythmes corticaux induits par une stimulation lumineuse intermittente. *Marseille Med.*, **1947**, *5*: 240-248.

WALTER, V. J. and WALTER, W. GREY. The central effects of rhythmic sensory stimulation. *EEG Clin. Neurophysiol.*, **1949**, *1*: 57-86.

WEIL, A. A. Non-sleep electroencephalogram activation. *Dis. Nerv. Syst.*, **1952**, *13*: 11-16.

WEIL, A. A. and NOSIK, W. A. Photic stimulation in hemianopsia. *EEG Clin. Neurophysiol.*, **1952**, *4*: 219-222.

Reference: KOOI, K. A., ECKMAN, H. G. and THOMAS, M. H. Observations on the response to photic stimulation in organic cerebral dysfunction. *EEG Clin. Neurophysiol.*, **1957**, *9*: 239-250.

PRINTED IN CANADA

THE EFFECT OF THIOPENTAL SODIUM AND PENTYLENETETRAZOLE ON THE CORTICAL AND SUBCORTICAL RESPONSE TO PHOTIC STIMULATION IN THE CAT [1]

DONALD A. JOHNSON, Ph.D.[2] and REGINALD G. BICKFORD, M.B.

Section of Physiology, Mayo Clinic and Mayo Foundation, Rochester, Minn.

(Received for publication: August 9, 1956)

This study was undertaken in an attempt to establish the reliability of methods to be used in later experiments aimed at elucidating the neural pathways involved in the myoclonic response to photic stimulation. It had been suggested (Gastaut and Hunter 1950) that measurements of the latent period of responses to photic stimulation permit deductions concerning the route traveled by the light impulse through the nervous system.

It is clear that, if measurements of the latent period of responses to photic stimulation are to be used to determine the pathways followed by the light impulse through the brain under conditions of pentylenetetrazole (Metrazol) activation, a thorough investigation of factors influencing such latent periods should be carried out as a preliminary study. Therefore we studied the influence of (1) barbiturate anesthesia and (2) pentylenetetrazole (and barbiturate anesthesia) on measurements of the latent period of responses at various points in the visual pathway.

A review of the literature indicated that the effect of anesthesia on responses evoked by photic stimuli had not been studied intensively. This is particularly true in relation to the latent period of such responses. The studies in the literature indicate that (1) evoked responses persist after all spontaneous activity has been suppressed by barbiturate anesthesia (Bremer 1937; Derbyshire *et al.* 1936; Marshall, Woolsey and Bard 1941; Woolsey 1947); (2) the primary wave is more resistant to the effects of anesthesia than are the other portions of the evoked response (Adrian 1941; Bremer 1937; Derbyshire *et al.* 1936; Forbes *et al.* 1949; Marshall, Talbot and Ades 1943; Marshall, Woolsey and Bard 1941); (3) the refractory period, after an evoked response, is prolonged in deep barbiturate anesthesia (Beecher, McDonough and Forbes 1938; Gastaut *et al.* 1951; Jarcho 1949; Marshall 1938; Marshall 1941; Marshall, Woolsey and Bard 1941; Morin, Gastaut and Corriol 1951), and (4) the latent period is changed not at all or only slightly by very great changes in the depth of anesthesia (Forbes *et al.* 1949; Forbes and Morison 1939; Marshall 1938; Marshall 1941; Marshall, Woolsey and Bard 1941).

METHODS AND PROCEDURES

Material. Fifteen cats were used in this study. The initial anesthesia was induced by intraperitoneal or intravenous injection of thiopental sodium. Intraperitoneal injection (50 mg. per kilogram) was used only in a few of the early experiments, since it was found that the intravenous method afforded much better control over the depth of anesthesia than the intraperitoneal method. After the initial anesthetization, a small polythene catheter was placed in a saphenous vein. Additional thiopental sodium was administered through the catheter as desired. An intratracheal cannula was used routinely.

Operative Procedure. A wide craniotomy was done, exposing the entire superior aspect of both hemispheres in most cases. Mineral oil was used on the cortex to prevent drying. The head was held rigidly in a special plastic headholder or in the Horsley-Clark apparatus. The

---

[1] Abridgment of thesis submitted by Dr. Johnson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Neurosurgery.

[2] Fellow in Neurosurgery, Mayo Foundation. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

eyelids were held open by a suture in each upper lid with appropriate tension on the same. The nictitating membranes were removed surgically. The pupils were dilated with 1 per cent homatropine before the experiment was started. Cortical excisions were made by suction through a spinal needle with a blunt end. Bleeding was usually light and easily controlled.

After the animal was completely prepared, curarization was accomplished by means of intravenous injection of intocostrin. Then artificial respiration was started. Curare was given initially to the point of cessation of spontaneous respiration, then added periodically when spontaneous activity appeared in the record from the muscle electrodes. An electric lamp near the animal was used to maintain the body temperature.

Recording Technique. Chlorided silver electrodes were used to record from the cortex, and insulated copper electrodes were used for recording from the lateral geniculate and the optic nerve. The copper electrodes were made of no. 20 enameled wire and were bare for 1 to 1.5 mm. at the tip. Monopolar recording was used throughout, with the indifferent electrode placed in the posterior neck muscles. A ground was attached to the tracheal cannula.

Leads from the striate cortex were consistently placed near the middle of the lateral gyrus at the point giving the maximal response to photic stimulation at the beginning of the experiment. The electrode in the lateral geniculate was placed by recording continuously to the flashing light both on the oscillograph and by sound as the electrode was lowered into the brain, after the electrode had been oriented by surface markings known to overlie the lateral geniculate. A great increase in the amplitude of the response, accompanied by increased high-frequency hissing sounds when the electrode entered the lateral geniculate, was very characteristic. Usually only one or two trials were necessary to place this electrode accurately. Recording from the optic nerve was done by means of an electrode placed by direct visualization at the optic foramen, after resection of the appropriate frontal portion of the brain on one side. Muscle recordings were made from two needle electrodes in the right biceps group of muscles.

Electrical records were made simultaneously on a six-channel (Offner) ink-writing oscillograph and on a double-beam cathode-ray oscilloscope. On the ink-writing oscillograph the low-frequency compensation dial was set to a time constant of 0.02 second. Integrated brain potentials were recorded as described by Bickford (1950), to quantitate the changes in EEG (electroencephalographic) pattern associated with variation of the depth of anesthesia. The bias of the integrator tube was adjusted to a leakage value of not greater than 1 unit per minute with no signal input. Attenuation of the input was adjusted so that the largest anticipated signal would fall on the linear range of the integrator system. This record was made from an area of cortex outside the striate area (cruciate sulcus) in order that the spontaneous potentials might reflect changes in the depth of anesthesia uninfluenced by the evoked discharges.

Drug Administration. Thiopental sodium was used in a 5 per cent solution and given intravenously in amounts of 0.1 or 0.2 cc. at intervals of 4 to 6 min. in various experiments, but at a uniform rate in a given experiment, depending on the size of the animal. Pentylenetetrazole (a 5 per cent solution) was given intravenously at a rate of 0.1 cc. every 30 sec. to the desired end point.

The photographs of the oscillograph tracings were taken approximately 1 minute after the thiopental sodium had been given. This avoided the immediate peak reaction to the drug. Administration of thiopental sodium was repeated soon enough (according to the weight of the animal) to avoid the fluctuation of the evoked response due to falling concentration of the anesthetic. It was possible in this way to make the anesthetic depression a continuous process, at a fairly uniform rate.

Light Stimulation. The photic stimulator (Bickford and Moffet 1951) was placed 11 inches (about 28 cm.) in front of the cornea. No attempt was made to limit the area of illumination. The rate of stimulation was confined to 1 flash per sec. The duration of each flash was 50 microseconds to the peak.

The intensity of the photic stimulus was approximately 80,000 foot-candles. All experiments were done under conditions of dark adaptation.

Measurements of Latent Period. The oscillograph tracings recorded on photographic film were projected on graph paper and enlarged about 25 times for measurement of the latent periods. All measurements were made from the onset of the light flash (light artifact) to the onset of the primary evoked response. No observations were discarded unless the onset of the primary response was not apparent.

Histologic Control. The site of the geniculate electrode was marked by electrolysis. The brains were perfused with isotonic saline solution and then with a solution of formalin and 1 per cent potassium ferricyanide. After removal they were fixed in formalin for several days. The site of the depth electrode was identified grossly and also microscopically on thionine-stained tissue preparations.

RESULTS

Influence of Anesthesia on Latent Period. Our experiments have shown that the latent period of a response to a photic stimulus lengthens as the level of thiopental sodium anesthesia deepens. This effect of thiopental sodium on the latent period was observed in 15 different experiments on 15 animals.

The responses from the optic nerve were investigated in only a limited number of experiments and the full range of the latent period of these responses was not determined.

Responses From Striate Cortex. Figure 1 illustrates the EEG pattern during photic stimulation, in an experiment in which anesthesia was progressively deepened by adding 10 mg. of thiopental sodium intravenously at intervals of 5 min. When the experiment was begun, the EEG record (fig. 1 A-RC) indicated that the animal was in the second stage of thiopental sodium anesthesia according to the classification of Kiersey, Bickford and Faulconer (1951). The record from the lateral gyrus (LL) shows a response to each light flash (L). The evoked response consisted of a primary response and two after-responses and is shown more clearly in the oscillograph tracing (fig. 1 F-A). The latent period of the response illustrated by tracing F-A was 17 msec.

Figure 1 A to E and figure 2 A to E show the changes of the EEG record and the mean latent period of the striate response to photic stimulation, at corresponding points in the experiment, as thiopental sodium anesthesia was progressively deepened. The EEG records, A, B, and C of figure 1 show hardly any change on visual examination, while the corresponding determinations of the mean latent period of the striate response (fig. 2 A, B and C) increased progressively as thiopental sodium was given. The after-responses shown in F-A of figure 1 were suppressed between A and B of figures 1 and 2.

EEG records D and E of figure 1 show progressive depression of spontaneous cortical activity as more thiopental sodium was given. The "projection activity" of Morison and Dempsey is prominent in E. The mean latent period of the cortical response to light, at this stage of the experiment, increased progressively (fig. 2 D and E) during the same period.

Oscillograph tracing F-B of figure 1 was photographed at the stage of the experiment represented by E of figures 1 and 2. The after-responses were suppressed, the amplitude of the response was diminished and the latent period was 25 msec.

The experiment illustrated in figures 1 and 2 is representative of the gradual lengthening of the latent period and changing characteristics of the cortical response to photic stimulation that we have seen during progressive thiopental sodium anesthesia. The range for the latent period of the cortical response is somewhat wider than demonstrated in this experiment. It is noteworthy that the mean latent period may change progressively while the EEG pattern is essentially unchanged to visual inspection.

In these experiments it was observed that when the latent period of striate response exceeded 25 msec. the spontaneous activity of the cortex was completely suppressed.

It was apparent that one could quantitatively relate the change in the latent period of the evoked response in the visual

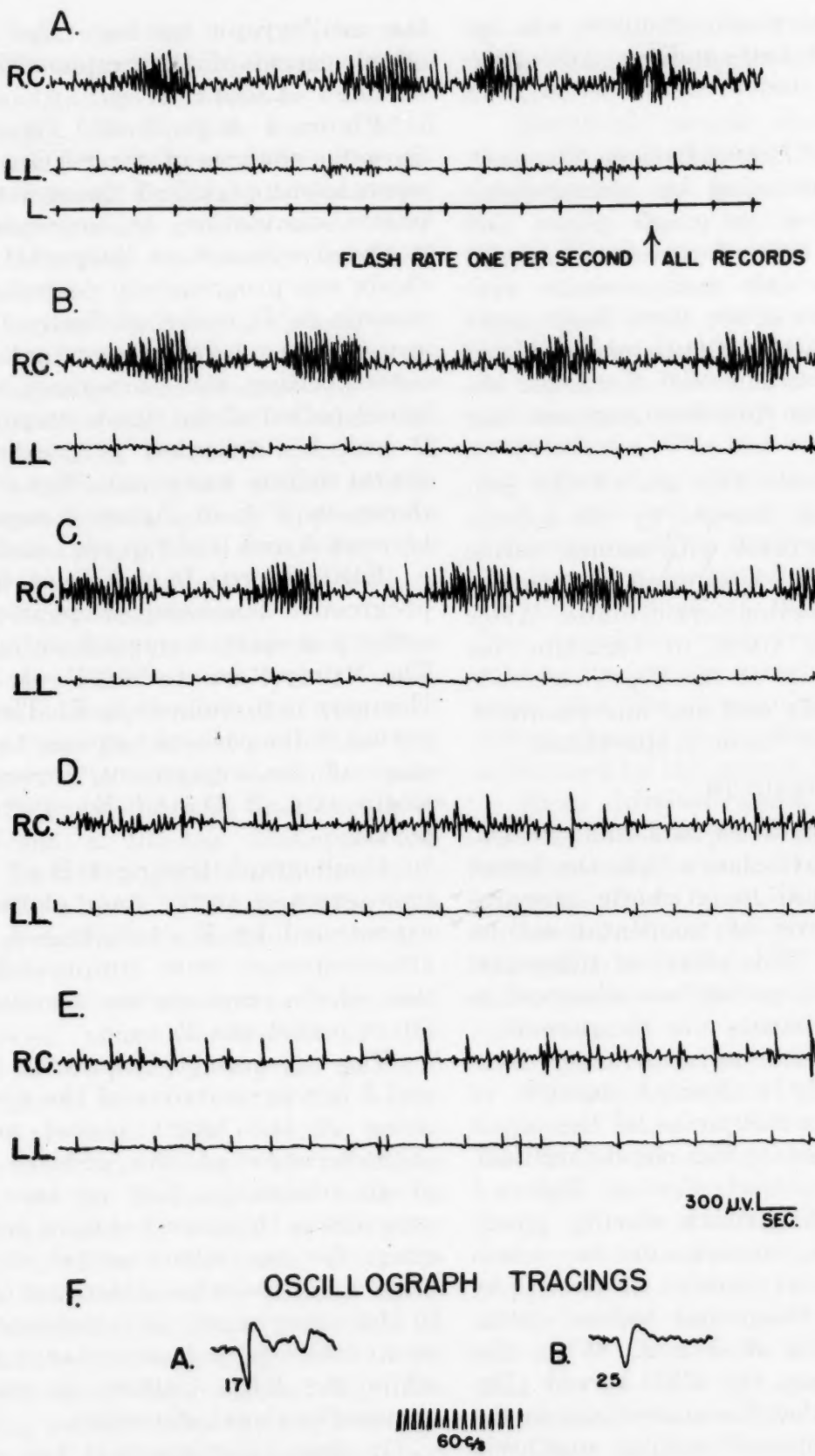


Fig. 1

EEG records in progressive thiopental sodium anesthesia A-E. Right cruciate sulcus (RC), left lateral gyrus (LL), light flash (L). Oscillograph tracings F-A and F-B are evoked responses from the left lateral gyrus taken at the beginning and end of the experiment and correspond to EEG records A and E respectively. The number below each tracing is the latent period in milliseconds. Cat weighing 3.7 kg. was anesthetized initially with thiopental sodium (50 mg. per kilogram, intraperitoneally). Thiopental sodium given intravenously at rate of 10 mg. at 5-min. intervals.

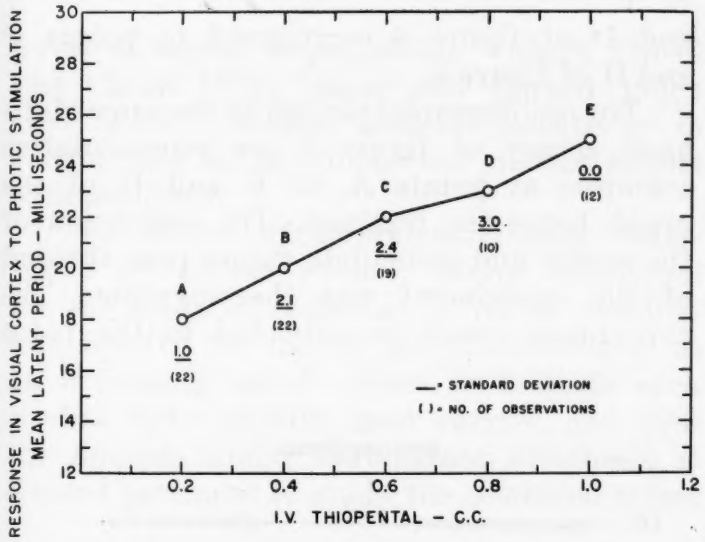


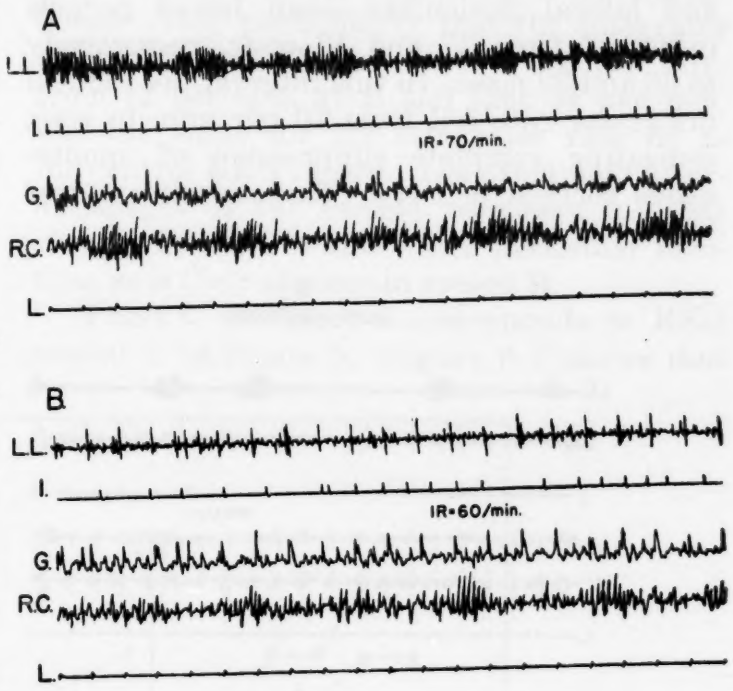
Fig. 2

Mean latent periods of the cortical response to light stimulation, during progressive thiopental sodium anesthesia. The intensity of stimulus was about 80,000 foot-candles. Same experiment as illustrated in figure 1; letters A to E on the two figures indicate observations at the same stage of the experiment.

pathway to the amount of thiopental sodium given, and also to the stages of EEG activity in thiopental sodium anesthesia. However, a more precise measure of the changes in cortical activity associated with progressive narcosis was desirable. It was decided therefore to use the electronic integration method of Bickford (1950) to quantify the changes in the EEG pattern associated with variation of the depth of anesthesia. An experiment in

Fig. 3

Relation of the mean latent period of responses from the lateral geniculate and the striate cortex, during photic stimulation, to the integrator rate per minute. Progressive thiopental sodium anesthesia. Oscillographic tracings are representative examples of evoked responses at the corresponding points on the graph. The number under each tracing is the measurement of the latent period in milliseconds.



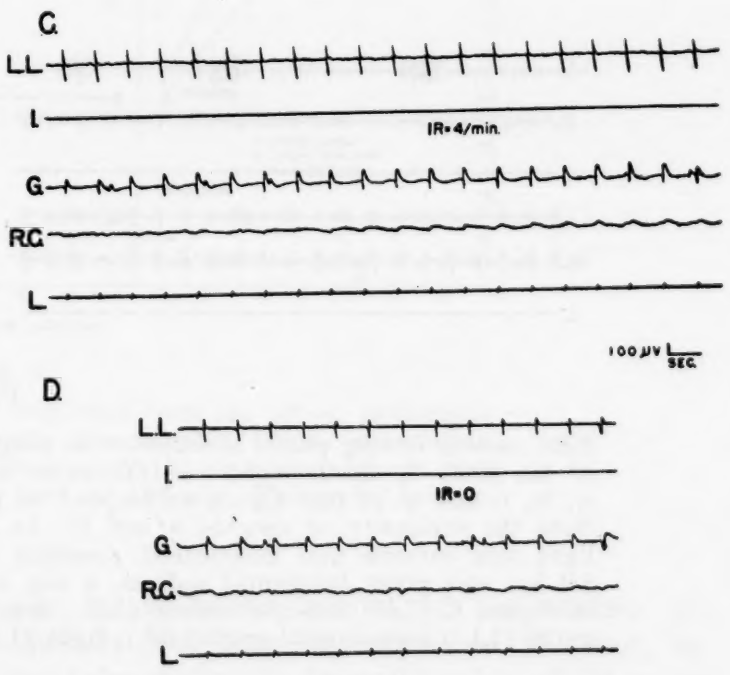


Fig. 4

EEG records during photic stimulation in progressive thiopental sodium anesthesia. From the same experiment illustrated in figure 3. EEG records A and B correspond to points A and B of figure 3. EEG records C and D correspond to points F and H respectively of figure 3. Animal weighed 5 kg. Thiopental sodium intravenously, 5 mg. at 5-min. intervals after the initial anesthetization. Left lateral gyrus (LL), integrator (I), lateral geniculate (G), light flash (L), integrator rate (IR), right cruciate sulcus (RC).

which the spontaneous activity was quantitated in this way is illustrated in figure 3.

In the course of this experiment, the striate and lateral geniculate mean latent periods increased from 17 and 15 msec. respectively to 36 and 32 msec. In this interval the cortical integrator rate fell from 70 per min. to zero, indicating complete suppression of spontaneous cortical activity. The experiment was carried somewhat beyond this point, as indicated by the values at H in figure 3. Striate and geniculate values ran parallel until near the end of the experiment. EEG and integrator activity corresponding to these latency measurements is shown in figure 4. EEG records A and B of figure 4 correspond to points A and B of figure 3; EEG records C and D of figure 4 correspond to points F and H of figure 3.

The oscillograph tracings in the upper left-hand corner of figure 3 are representative examples at points A, C, F and H of the graph below the tracings. The separation of the striate and geniculate values near the end of the experiment was characteristic. The experiment could be extended to the point where a cortical response to the photic stimulus was no longer evoked, whereas a geniculate response was still prominent. If more thiopental sodium was given, the evoked response in the lateral geniculate could be suppressed, whereas a response was still recorded from the optic nerve. This indicated a selective sensitivity to anesthesia at different

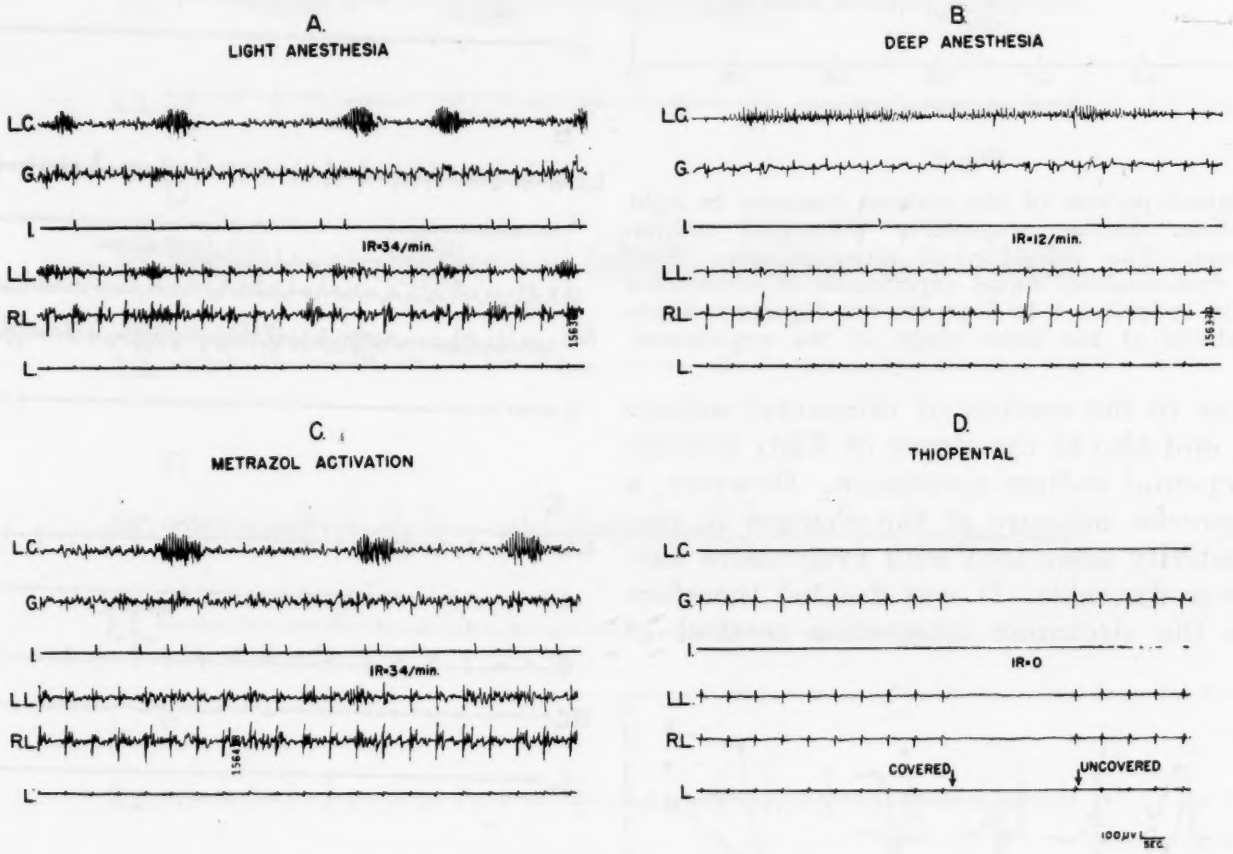


Fig. 5

EEG records during photic stimulation in progressive thiopental sodium anesthesia. Activation of the EEG by intravenous administration of pentylenetetrazole (Metrazol). EEG records A, B, C and D of this figure correspond to points A, B, C and D respectively of figure 6. Note the similarity of records A and C. In D, evoked responses ceased promptly when the light was covered and reappeared promptly when the light was uncovered. Cat weighing 2.9 kg. was given thiopental sodium, 5 mg. at 5-min. intervals. Pentylenetetrazole as noted in figure 6. Left cruciate sulcus (LC), lateral geniculate (G), integrator (I), left lateral gyrus (LL), right lateral gyrus (RL), light (L), integrator rate (IR).

levels of neural organization. Others (Noell and Chinn 1950; Sugar and Gerard 1938) have noted a similar selective sensitivity to anoxia, and we have observed similar results with asphyxia.

The Effect of Pentylenetetrazole (Metrazol) on Latent Period. Many techniques for the study of responses to photic stimulation involve the use of pentylenetetrazole as an activating agent. Since in animals such studies have usually been carried out with the animals under barbiturate anesthesia it seemed pertinent to study the combined effect of the two agents on latent periods of responses to photic stimulation. These two chemical substances are, of course, well known to be somewhat antagonistic in their physiologic effects. Figures 5 and 6 represent an experiment demonstrating the effect of pentylenetetrazole on an animal subjected to progressive thiopental sodium anesthesia.

Figure 5 A and B shows the change in the EEG record and integrator rate with anesthesia. Figure 5 C is the EEG record after pentylenetetrazole had been given intravenously, 2.4 cc. over the course of 12 min. Compare EEG record C with record A, the control record at the beginning of the experiment. Note particularly that the integrator rate of record C increased to 34 per min. from 12 per min. at B and that 34 per min. was the value for the integrator rate in A, the control EEG record. The prominent afterdischarges of the evoked responses in EEG records A and C is also worth particular mention, as is their absence in record B.

Point C of figure 6 corresponds to EEG record C of figure 5. Figure 6 C shows that the mean latent period of the striate responses had been shortened to 17 msec. by pentylenetetrazole from its value of 24 msec. at B (compare with fig. 5 B). The latent period of the geniculate response was not shortened. This was not surprising, since it was already a fairly short value for geniculate responses to photic stimuli. This effect of pentylenetetrazole, causing a reversal of the EEG pattern and shortening of the latent period after progressive thiopental sodium narcosis, was demonstrated in 10 different

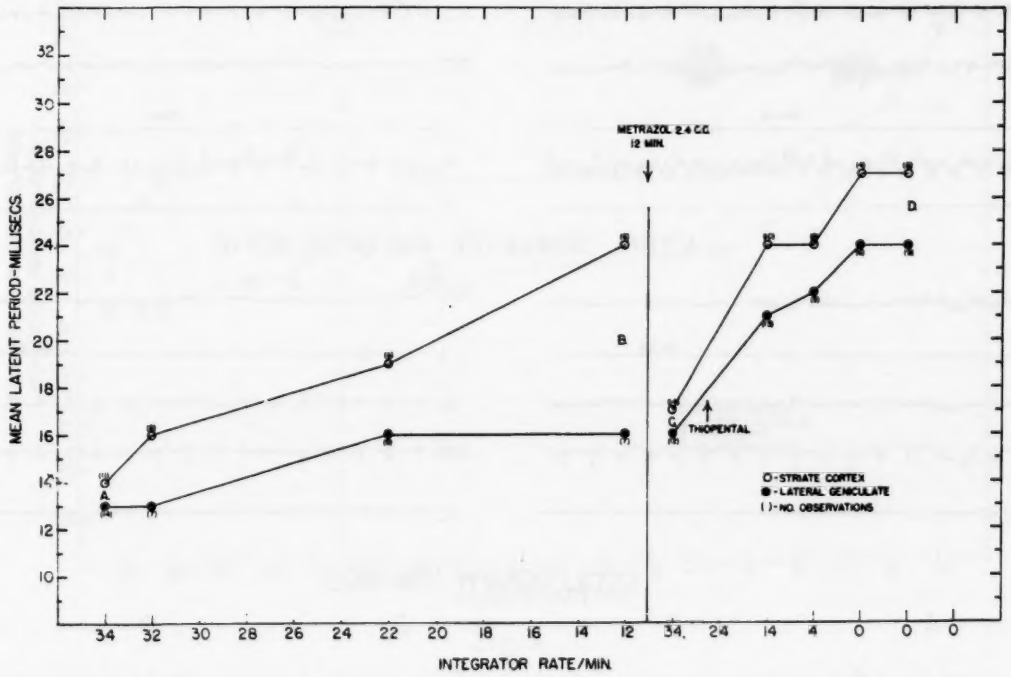


Fig. 6

Relation of the mean latent period of responses from the lateral geniculate and striate cortex to the integrator rate per minute. Photic stimulation in progressive thiopental sodium anesthesia. At B pentylenetetrazole was given, 5 mg. at 30-sec. intervals to a total of 120 mg. Thiopental sodium was given again after C.

experiments. Pentylenetetrazole did not reverse the EEG pattern and shorten the latent periods if thiopental sodium depression was carried beyond the point of complete suppression of spontaneous cortical activity and beyond the point at which the latent period of the striate response had increased to 25 msec.

Figure 6 C to D shows the progressive increase of the latent periods of the evoked responses as thiopental sodium was given again. EEG record D of figure 5 shows the corresponding depression of spontaneous activity.

Figures 7 and 8 illustrate another experiment in which there was a gradual decrease of the cortical integrator rate and increase of the mean latent period of the striate and geniculate responses as thiopental sodium was given. EEG records A and B of figure 7 and oscillograph tracings A and B represent the first phase of the experiment. The change of the mean latent period of the striate and geniculate responses during this phase of the experiment is shown graphically in figure 8 A to B.

Between points B and C of figures 7 and 8 frontal brain resection was done unilaterally and an electrode was placed directly on an optic nerve. A small amount of pentylenetetrazole (30 mg.) was given in order to counteract to some extent the depression necessarily incident to resection of a frontal lobe.

After these procedures, the mean latent

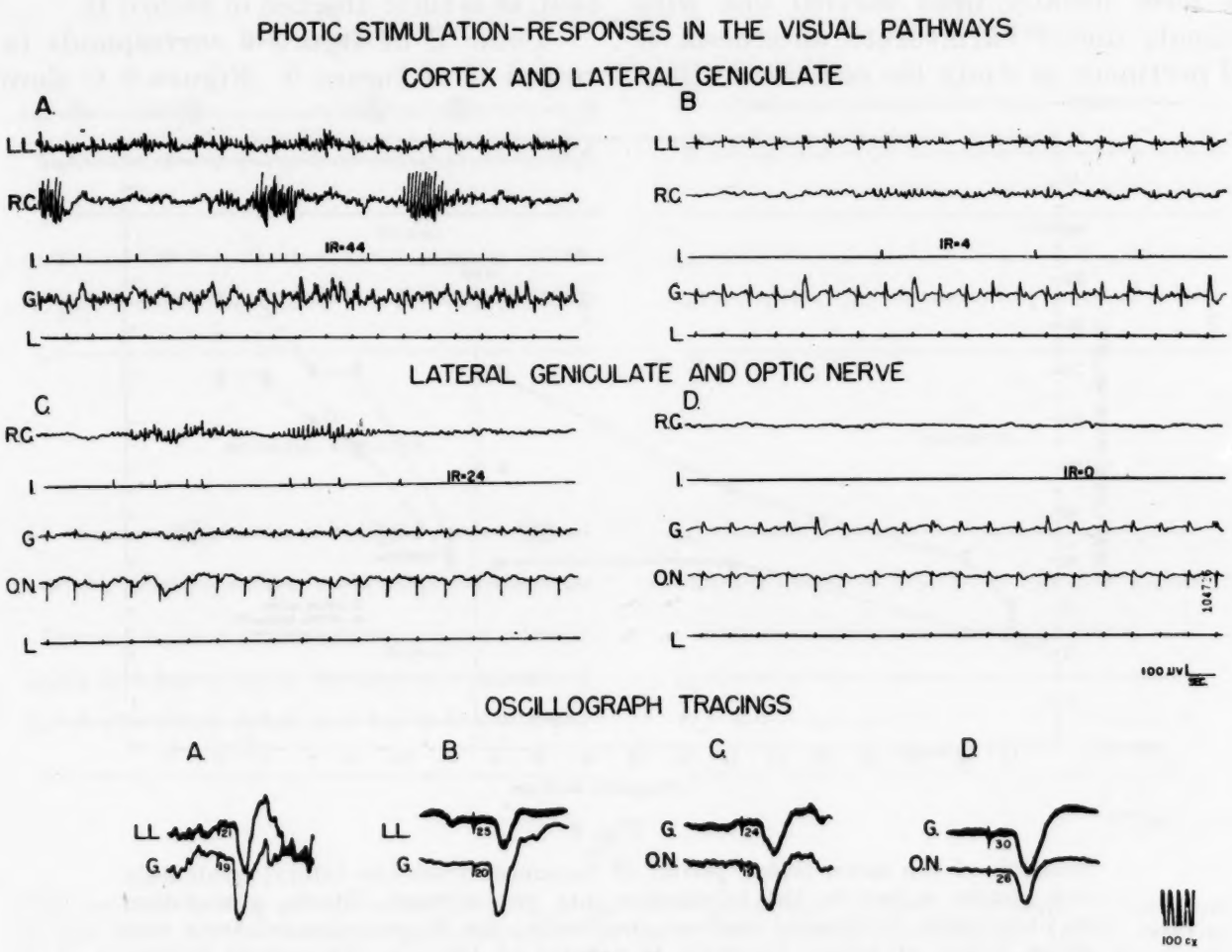


Fig. 7

EEG records of responses in the visual pathways during photic stimulation and progressive thiopental sodium anesthesia. EEG records A, B, C and D correspond to oscillograph tracings A, B, C and D of the same figure and to points A, B, C and D respectively of figure 8. Pentylenetetrazole was given between B and C as indicated in figure 8. Cat weighed 2.7 kg. Thiopental sodium was given, 5 mg. at 5-min. intervals after the initial anesthetization. Left lateral gyrus (LL), right cruciate sulcus (RC), integrator (I), integrator rate (IR), lateral geniculate (G), light (L), optic nerve (ON).

period of the lateral geniculate response was 21 msec. and the latent period of the optic-nerve response was 17 msec., as shown in figure 8 C. The integrator rate was back to 24 per min. as a result of the pentylenetetrazole. The EEG record at this point is shown in figure 7 C. The oscillograph tracings at C of figure 7 were taken a few seconds later when additional thiopental sodium had raised the mean latent periods to 24 and 19 msec. respectively for the geniculate and optic-nerve responses to photic stimuli.

The part of the graph extending from C to D of figure 8 is similar to those discussed previously and shows the gradual increase of the mean latent periods and decrease of the cortical integrator rate in progressive thiopental sodium narcosis. The EEG records (C and D) and oscillograph tracings (C and D) of figure 7 correspond to the mean determinations of latent period for the geniculate and optic-nerve response at points C and D of figure 8. The interval between the geniculate and optic-nerve responses was essentially the same from the beginning to the end of the series of records. At point D of figure 8 the mean latent period of the lateral geniculate response was 30 msec. and that of the optic-nerve response 27 msec. The responses in the optic nerve were studied in only three experiments. Thiopental sodium prolonged the latent period of the optic-nerve response in each experiment. The observations in these experiments suggested that the effect of thiopental sodium anesthesia on this part of the visual pathway was similar to that observed in the cortex and lateral geniculate. In two experiments it was demonstrated that narcosis could be carried to a point at which the geniculate response was eliminated completely while a response to photic stimulation persisted in the optic nerve. As mentioned previously, a similar relationship was seen between the geniculate and cortical responses, the latter being more sensitive to thiopental sodium than the former. In addition it is noteworthy that when thiopental sodium was given in the early stages of a given experiment, the latent period of the cortical response was always the first to increase.

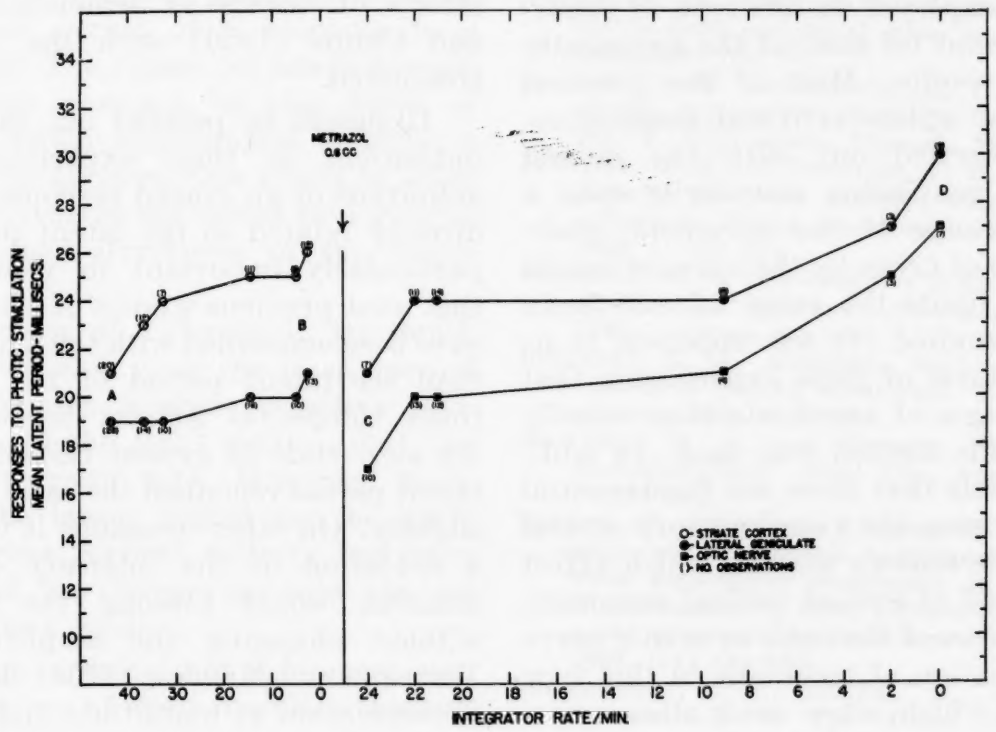


Fig. 8

Relation of the mean latent period of responses in the optic nerve, lateral geniculate and striate cortex to the integrator rate per minute in progressive thiopental sodium narcosis. Pentylenetetrazole, 30 mg., was given at the usual rate after exposure of the optic nerve at B.

COMMENT

These experiments indicate a progressive increase in latent period of the lateral geniculate and striate-area responses to photic stimuli with increasing depth of thiopental sodium anesthesia. This is in contrast to reports in the literature wherein it is stated that the latent period of evoked responses is not affected by the depth of anesthesia (Derbyshire *et al.* 1936; Forbes *et al.* 1949; Marshall 1938). It appears that differences in the technique employed in this type of experiment may account for some of the apparently contradictory results. Most of the previous studies did not utilize artificial respiration. Experiments carried out with the animal under natural ventilation necessarily span a more limited range of the anesthetic state. Administration of drugs by the intraperitoneal route likewise limits the range of anesthesia which can be studied. It was apparent to us early in the course of these experiments that the "light" stages of anesthesia were usually missed when this method was used. In addition it is probable that there are fundamental differences between the visual sensory system and the somatic sensory system, which affect the latent period of evoked central responses. Direct stimulation of the optic or sciatic nerve is another variation of technique in this type of experiment, which, when used, alters measurements of latent periods by virtue of elimination of the peripheral receptor.

The range of the latent period of responses to retinal stimulation recorded in these experiments is greater than that reported previously by others (Bartley and Bishop 1942; Bernhard 1940; Gastaut and Hunter 1950; Gerard, Marshall and Saul 1936; Marshall, Talbot and Ades 1943; Wang 1934). The relationship of the latent period to the depth of anesthesia as reported here doubtless explains the lack of uniformity of the measurements previously reported. The present findings are, however, in accord with the observations made on latencies under Pentothal anesthesia by Hunter and Ingvar (1955).

While changes in retinal delay time may have contributed to the over-all delay times measured in our experiments, it seems unlikely that this was a significant factor. This conclusion is based on the following reasons: (1) the latent period of the cortical response always changed first and often increased progressively, while the latent period of the geniculate response remained the same (fig. 6 A to B; fig. 7 A to B); (2) complete failure of cortical and geniculate responses occurred when optic nerve responses were still prominent, and (3) the effects of thiopental sodium were strikingly similar to the effects of anoxia as demonstrated by Noell and Chinn (1950) with the retinal factor eliminated.

It should be pointed out that there were indications in these experiments that the amplitude of an evoked response is not always directly related to the latent period. This is particularly important in view of the fact that most previous studies of evoked responses have been concerned with the amplitude rather than the latent period of the response. At times thiopental sodium actually increased the amplitude of evoked responses, while the latent period remained the same or lengthened slightly. On other occasions it was noted that a reduction of the intensity of the photic stimulus would prolong the latent period without changing the amplitude. French, Verzeano and Magoun (1953) have also noted a dissociation of amplitude and latent-period changes in anesthesia, though their study did not deal primarily with these changes.

In our experiments the geniculate-cortex response time interval increased as well as the geniculate and cortical response latent periods. The usual geniculate-cortex interval at the beginning of an experiment was about 1 msec. (This agrees with other reports: Chang, 0.8 msec.; Gastaut and Hunter, 1.0 msec.; Bishop and O'Leary, 0.5 msec.). This is best shown in figure 6, as is the tendency for the interval to lengthen out to about 3 msec. for the greater part of the experiment. The increase of the interval is roughly proportional to the increase of the latent periods, suggesting that conduction generally was affected.

The failure of the cortical response while a response was still evoked from the lateral geniculate conforms with the general impres-

sion that the cortex is affected most severely by barbiturates. The gradual progression of the depression to the lateral geniculate and then to the optic nerve suggests a metabolic effect to which the optic nerve is most resistant. The similarity of this sequence of events to that seen in anoxia and asphyxia indicates that the metabolic effects involve deficient oxygen utilization primarily.

It is apparent from our observations that both thiopental sodium and pentylenetetrazole alter the latent period of a response to a photic stimulus. The values for latent periods are considerably changed by the depth of anesthesia at which spontaneous activity is suppressed. Furthermore this effect is selective in that it involves the cortex to a greater degree than other structures in the visual pathways.

As an indicator of a change in the depth of anesthesia, the change of the latent period of evoked responses is more sensitive than visible changes in the EEG pattern, but less so than the integrator rate. However, measurements of the latent period can be made after spontaneous cortical activity has been suppressed and the integrator rate can no longer be used as a guide.

The findings indicate that inferences concerning the routing of light impulses through central nervous structures based on measurements of latent period are likely to be invalid unless these are made simultaneously or special precautions are taken to control anesthesia level during the period of observations.

SUMMARY

1. The effect of thiopental sodium (Pentothal) anesthesia and pentylenetetrazole (Metrazol) in changing the latency of the photic response at various levels of the optic system (optic nerve, geniculate and striate cortex) has been investigated. The anesthesia level has been quantitated by the method of cortical potential integration. With deepening thiopental anesthesia, there is progressive increase in latency at all three levels, with greatest increase at the cortex (for example, from 17 msec. to 36 msec. in one experiment).

2. Pentylenetetrazole reversed more or less completely the increase in latency caused by thiopental sodium.

3. The integrator rate is a more sensitive measure of depth of anesthesia than the cortical photic latency, but the latter can be used at a depth of anesthesia which invalidates integrator readings owing to total suppression of cortical activity.

REFERENCES

ADRIAN, E. D. Afferent discharges to the cerebral cortex from peripheral sense organs. *J. Physiol.*, **1941**, *100*: 159-191.

BARTLEY, S. H. and BISHOP, G. H. Some features of the optic-nerve discharge in the rabbit and cat. *J. Cell. Comp. Physiol.*, **1942**, *19*: 79-93.

BEECHER, H. K., MCDONOUGH, F. K. and FORBES, A. Effects of blood pressure changes on cortical potentials during anesthesia. *J. Neurophysiol.*, **1938**, *1*: 324-331.

BERNHARD, C. G. Contributions to the neurophysiology of the optic pathway. *Acta physiol. scandinav.*, **1940**, *1* (suppl. 1): 1-94.

BICKFORD, R. G. Automatic electroencephalographic control of general anesthesia. *EEG Clin. Neurophysiol.*, **1950**, *2*: 93-96.

BICKFORD, R. G. and MOFFET, W. T. A simple photostimulator. *EEG Clin. Neurophysiol.*, **1951**, *3*: 251-252.

BREMER, F. Différence d'action de la narcose éthérique et du sommeil barbiturique sur les réactions sensorielles acoustiques du cortex cérébral. Signification de cette différence en ce qui concerne le mécanisme du sommeil. *C. R. Soc. biol.*, **1937**, *124*: 848-852.

DERBYSHIRE, A. J., REMPEL, B., FORBES, A. and LAMBERT, E. F. The effects of anesthetics on action potentials in the cerebral cortex of the cat. *Amer. J. Physiol.*, **1936**, *116*: 577-596.

FORBES, A., BATTISTA, A. F., CHATFIELD, P. O. and GARCIA, J. P. Refractory phase in cerebral mechanisms. *EEG Clin. Neurophysiol.*, **1949**, *1*: 141-175.

FORBES, A. and MORISON, B. R. Cortical response to sensory stimulation under deep barbiturate narcosis. *J. Neurophysiol.*, **1939**, *2*: 112-128.

FRENCH, J. D., VERZEANO, M. and MAGOUN, H. W. A neural basis of the anesthetic state. *Arch. Neurol. Psychiat.*, Chicago, **1953**, *69*: 519-529.

GASTAUT, H., GASTAUT, Y., ROGER, A., CORRIOL, J. et NAQUET, R. Etude électrographique du cycle d'excitabilité cortical. *EEG Clin. Neurophysiol.*, **1951**, *3*: 401-426.

GASTAUT, H. and HUNTER, J. An experimental study of the mechanism of photic activation in idiopathic epilepsy. *EEG Clin. Neurophysiol.*, **1950**, *2*: 263-287.

GERARD, R. W., MARSHALL, W. H. and SAUL, L. J. Electrical activity of the cat's brain. *Arch. Neurol. Psychiat.*, Chicago, **1936**, *36*: 675-735.

HUNTER, J. and INGVAR, D. H. Pathways mediating Metrazol induced irradiation of visual impulses: an experimental study in the cat. *EEG Clin. Neurophysiol.*, **1955**, *7*: 39-60.

JARCHO, L. W. Excitability of cortical afferent systems during barbiturate anesthesia. *J. Neurophysiol.*, **1949**, *12*: 447-457.

KIERSEY, D. K., BICKFORD, R. G. and FAULCONER, A., JR. Electro-encephalographic patterns produced by thiopental sodium during surgical operations: Description and classification. *Brit. J. Anaesth.*, **1951**, *23*: 141-152.

MARSHALL, W. H. The effect of anesthesia on the responses of central sensory systems. *Amer. J. Physiol.*, **1938**, *123*: 140-141.

MARSHALL, W. H. Observations on subcortical somatic sensory mechanisms of cats under Nembutal anesthesia. *J. Neurophysiol.*, **1941**, *4*: 25-43.

MARSHALL, W. H., TALBOT, S. A. and ADES, H. W. Cortical response of the anesthetized cat to gross photic and electrical afferent stimulation. *J. Neurophysiol.*, **1943**, *6*: 1-15.

MARSHALL, W. H., WOOLSEY, C. N. and BARD, P. Observations on cortical somatic sensory mechanisms of cat and monkey. *J. Neurophysiol.*, **1941**, *4*: 1-24.

MORIN, G., GASTAUT, H. et CORRIOL, J. Cycle d'excitabilité du cortex visuel primaire chez le chat. *C. R. Soc. biol.*, **1951**, *145*: 918-919.

NOELL, W. and CHINN, H. I. Failure of the visual pathway during anoxia. *Amer. J. Physiol.*, **1950**, *161*: 573-590.

SUGAR, O. and GERARD, R. W. Anoxia and brain potentials. *J. Neurophysiol.*, **1938**, *1*: 558-572.

WANG, G. H. Action potentials of the visual cortex and the superior colliculus induced by stimulation of the retina with light. *Chinese J. Physiol.*, **1934**, *8*: 121-141.

WOOLSEY, C. N. Patterns of sensory representation in the cerebral cortex. *Fed. Proc.*, **1947**, *6*: 437-441.

Reference: JOHNSON, D. A. and BICKFORD, R. G. The effect of thiopental sodium and pentylenetetrazole on the cortical and subcortical response to photic stimulation in the cat. *EEG Clin. Neurophysiol.*, **1957**, *9*: 251-262.

PRINTED IN CANADA

A LONGITUDINAL STUDY OF ELECTROENCEPHALOGRAPHIC FREQUENCY PATTERNS IN MENTAL HOSPITAL PATIENTS AND NORMAL CONTROLS [1]

MARGARET A. KENNARD, M.D.[2] and ALEX E. SCHWARTZMAN, Ph.D.[2]
Department of Neurological Research, University of British Columbia

(Received for publication: July 27, 1956)

In a previous paper (Kennard *et al.* 1955) it was reported that the overall EEG frequency patterns of groups of individuals having different personality characteristics showed significant differences, and that, furthermore, these EEG patterns could be correlated with specific personality attributes. Thus, the number of individuals in penal institutions who showed a high peak of EEG alpha activity was significantly high as compared to that of a normal group, and almost no schizophrenic patients in a mental hospital produced such pure alpha activity. Various specific attributes of frequency pattern could, in addition, be related to specific personality qualities as delineated by psychological tests (Kennard *et al.* 1956; Rabinovitch *et al.* 1955).

During these preliminary investigations, two other factors appeared to be significant: (*a*) many of those patients who were acutely and severely ill on admission seemed to have very severely distorted EEG frequency patterns; (*b*) in some instances when a second record was made there was a change in this EEG pattern during hospital stay. The present investigation was, therefore, devised in order to test these two factors by means of a longitudinal study. In it 62 patients in a mental hospital and 25 normal controls have been examined repeatedly by EEG recordings and psychological examinations. The findings of the EEG study are reported here; those relating to the psychological data elsewhere (Schwartzman and Kennard 1956).

METHOD

The methods used in the present study are exactly those used and described in detail in the previous one (Kennard *et al.* 1955). Throughout the recordings the gain of the EEG frequency analyzer was routinely set at 7 and the gain for the EEG instrument at 7 mm. for 50 microvolts. No other attempt at calibration was made as with the existing instrumentation none was possible for the frequency analyzer. Thus, groups of subjects, types of psychological examinations and of EEG recordings were as exactly duplicated as possible. Briefly, the following limits were set for the investigation. All subjects were either patients in the Crease Clinic, Essondale, B.C., or control "normals" matched for age, sex and, roughly, for intellectual achievement. All were between the ages of 13 and 30 inclusive. All had I.Q.s above 80. All patients were first admissions to the Crease Clinic, which is that part of the Provincial Mental Hospital to which relatively lightly disturbed patients are received as residents for a period not longer than four months. About half were voluntary admissions. About 80 per cent were returned from the Clinic to their home environment. Half were diagnosed as schizophrenics, the other half being a mixed lot of non-psychotic patients; hysteria, neurosis or disorder of behavior being the most common diagnoses. Many of the latter group were only rather mildly maladjusted, and were discharged in due time, having shown some recovery as the result of their residency in the hospital. The schizophrenics all received insulin coma therapy between their first and second tests.

[1] Aided by a Federal Mental Health Grant and by the Mental Health Service, Province of British Columbia, Canada.

[2] Now at Mental Health Research Institute, Fort Steilacoom, Wash.

The patients were appraised psychologically, using a battery of tests also described previously (Kennard *et al.* 1955; Rabinovitch *et al.* 1955). The Rorschach and Wechsler-Bellevue tests were, in every instance, supplemented with special tests of various kinds.

EEG recordings were made from Grass eight-channel machines, according to the routine scanning which was necessary for clinical reasons. An Offner frequency analyser was used, measurements being made from bipolar recordings using 16 scalp areas, 8 to either side of the midline as shown in figures 2 and 4, and 8, more laterally, on either side about the temporal regions. For the purposes of the present paper only the more medial regions are to be discussed. Since the temporal areas showed much wider variations, analysis of their inter-relationships is not yet completed.

An EEG frequency graph for each patient was then made by measurement in centimeters of the height of pen deviation, i.e., the amount of energy or the voltage for each recorded frequency. These figures were then transmitted to two graphs, showing frequency curves, for each of the 16 recording areas; one graph, that discussed in this paper, being for the midline regions, frontal to occipital (fig. 2 and 4), and the other for the lateral temporal areas.

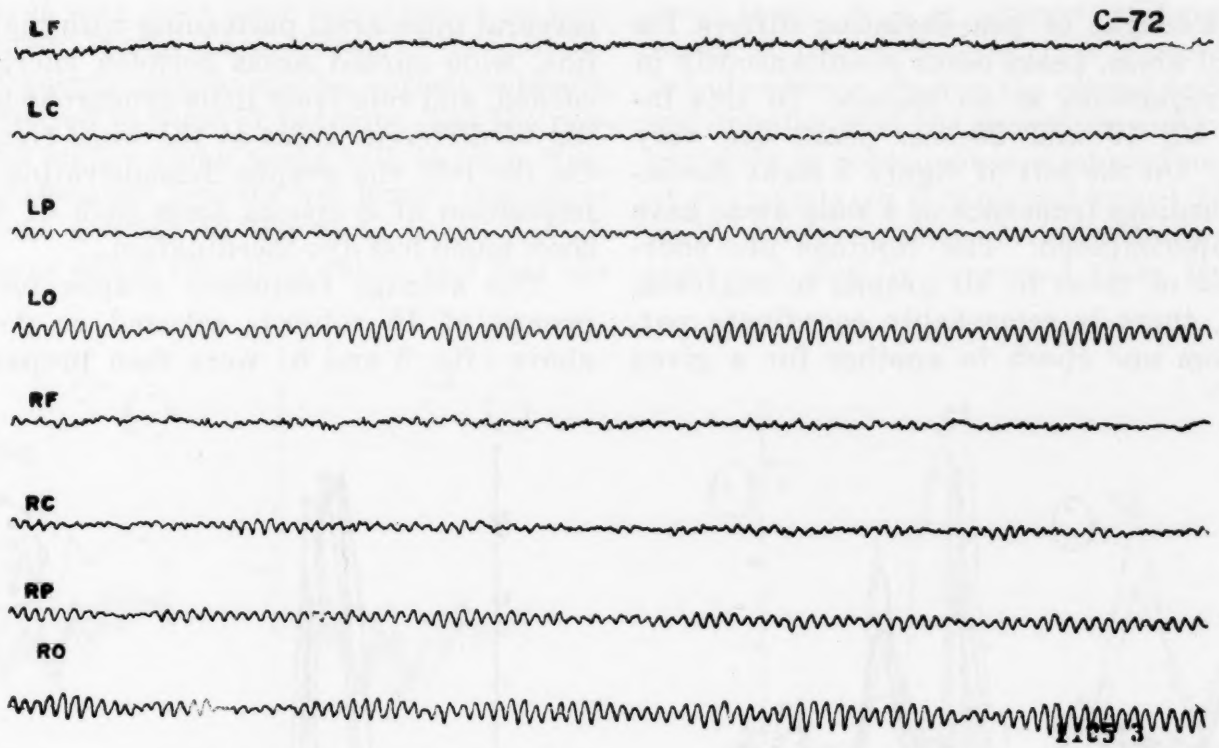
The graph averages shown in figures 5 and 6 were made by adding the figures for each frequency from the records of 15 individuals in each group. The selection of schizophrenic and non-psychotic groups was made by means of psychological examinations. Thus, each patient selected for inclusion in the averages was chosen because both clinical diagnosis and psychological tests showed all the criteria necessary for the specific group. Similarly, although the 25 members of the control group were all selected because they were in every way "normal", this group was eventually refined by use of the psychological tests to the first 15 cases examined who showed no marked deviation from the normal, according to the history and psychological appraisal.

Finally, the inspection method of appraisal of frequency graphs was used here as it had been previously (Kennard *et al.* 1955, 1956). The ten criteria previously found significant in comparing frequency graphs were again utilized and, again, appear to have value (fig. 7). Five of these criteria have to do with characteristic frequencies, alpha, theta, beta, 13-15/sec. and 16-18/sec. The other 5 relate to inter-area organization of cortical potentials: "good organization", "poor organization", "wide spread" of activity about the alpha area, "double alpha peak", and "left right dys-synchrony". All these are measured as objectively as possible according to specifications previously laid down (Kennard *et al.* 1955).

EEG recordings and psychological tests were always made within a day or two of each other, and, whenever possible, on the same day. All first tests were made during the first week after admission, and many during the first or second day. Repeat tests were then made on both controls and patients at the end of a month, and, in the case of many patients, an EEG was recorded a third, fourth and fifth time, depending on duration of hospital stay.

DATA

Figures 1 to 3 are presented to illustrate the type of information which can be added by a frequency graph to that produced by the EEG alone. The two EEGs of figure 1 have each a well-defined alpha, that of case C-72 being slightly more regular than that of case 99. There is little visible fast activity in either record and no true theta pattern. The frequency patterns (fig. 2 and 3), however, pick up much more marked differences. In figure 2 the frequency pattern of case C-72 appears as regular, of high alpha index, and without any of the inter-areal dys-coordination apparent in the frequency graph of case 99 (fig. 3). That the type of dys-coordination apparent in case 99 is largely inter-areal rather than due to irregularities of pattern from a single area is demonstrated in figures 2 and 4. Figure 2 (right) contains the very regular "normal" graph of frequencies from the eight recording areas of case C-72, which have been superimposed. It can be seen that,



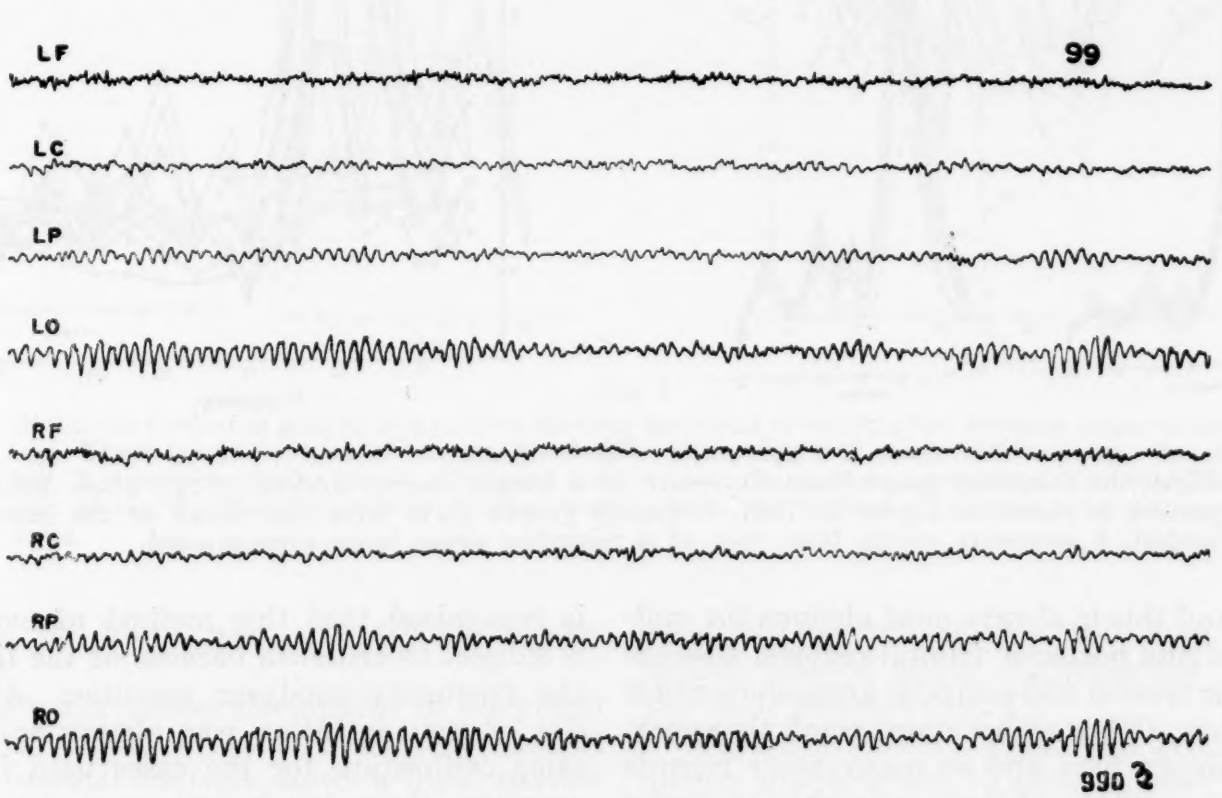


Fig. 1

Sample EEG records from two individuals who have each relatively marked alpha pattern but who show different types of frequency graphs (fig. 2 and 3).

although height of pen deviation differs for different areas, peaks occur simultaneously in given frequencies as do valleys. In this instance, 10, 16 and 20/sec. peaks are very obvious. On the left of figure 2 eight successive recordings from each of 4 scalp areas have been superimposed. The findings are characteristic of those in all graphs so analysed, namely, there is remarkably coordinate pattern from one epoch to another for a given cerebral inter-areal patterning with high baseline, wide spread areas between energies recorded, and relatively little synchronous peaking of different areas at the same frequency. On the left, the graphs demonstrating superimposition of 8 epochs from each of 4 areas show much less dys-coordination.

The average frequency graphs for the 4 groups of 15 subjects selected as described above (fig. 5 and 6) were then prepared. It

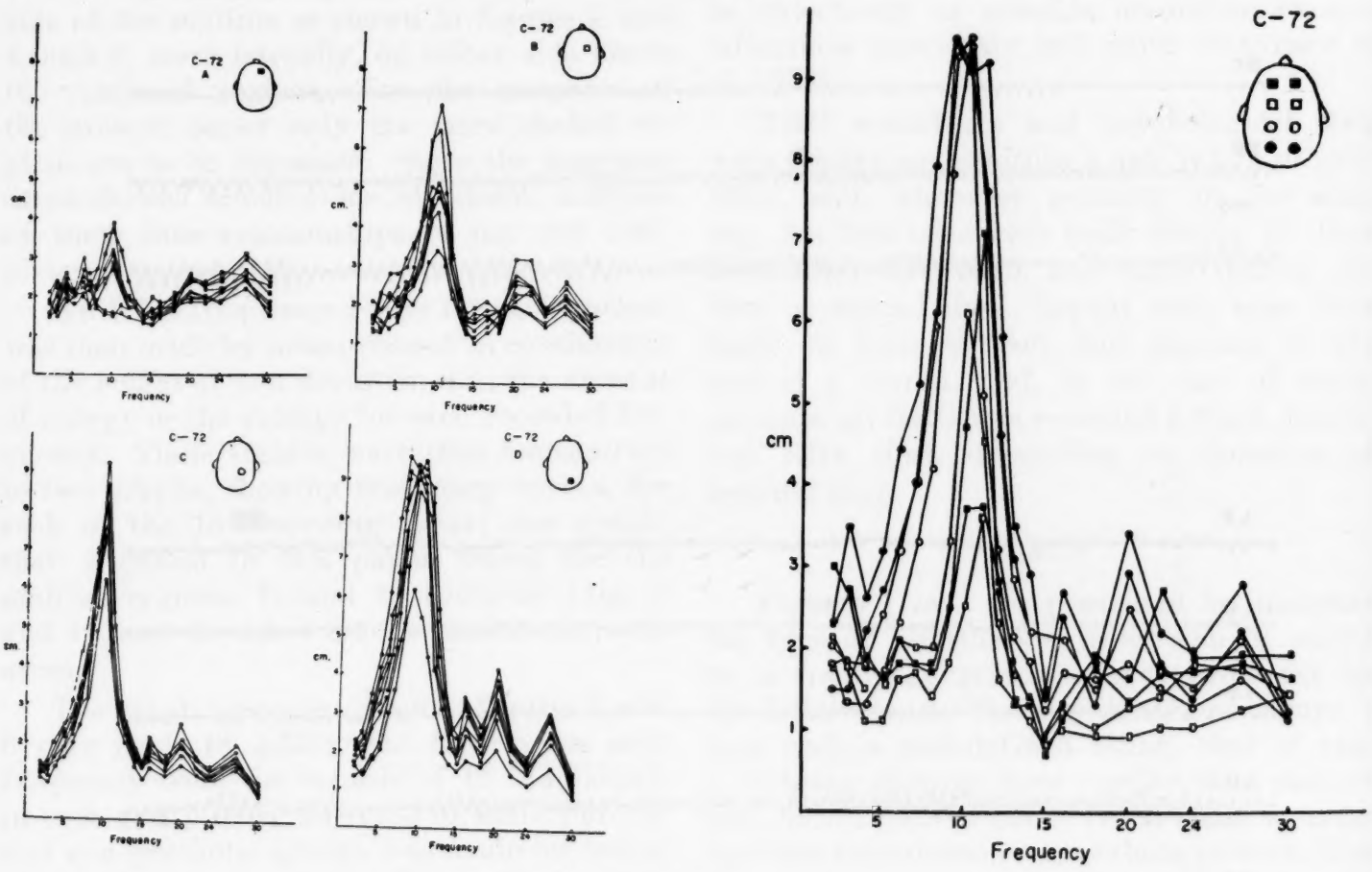


Fig. 2

Right, the frequency graph from the record of a normal control subject (C-72) whose EEG pattern is shown in figure 1. Left, frequency graphs made from the record of the same subject, 8 successive epochs from each of 4 recording areas being superimposed.

area; and this is always most obvious for mid-parietal and posterior frontal regions, whereas anterior frontal and occipital areas show wider variation. Other rather unexpected characteristics shown here and in many other records are: the emphasis of theta activity in posterior frontal (motor) regions, and the marked beta activity appearing in the occipital poles.

All these characteristics are seen again in figure 4 which shows (right) a disorganized

is recognized that this method of averaging is subject to criticism because of the limits of the frequency analyzer machine. Although size of pen deviation was always set at the same calibration for the cases used in these averages, there can be no exact quantitative data assembled which relates to size of pen deviation, i.e., energy level. On the other hand, the type of pattern produced in the different sub-groups is sufficiently different

so that it may have some significance as here presented. It was characteristic of the individual frequency graphs of the normal subjects, as compared to those of patients, that the normal had higher alpha peaks with sharper tips; that the baseline activity was lower; that there was some activity in the theta band, but almost none above the alpha rates; and that the more theta. It is of interest, and probably a result of poor technique, that a certain number of controls, during the second test, expressed impatience at the procedure and produced, probably in consequence, alpha-minus records of the unrelaxed but normal type. The effect on the average pattern is one of lowered alpha peak and slightly increased theta level. The

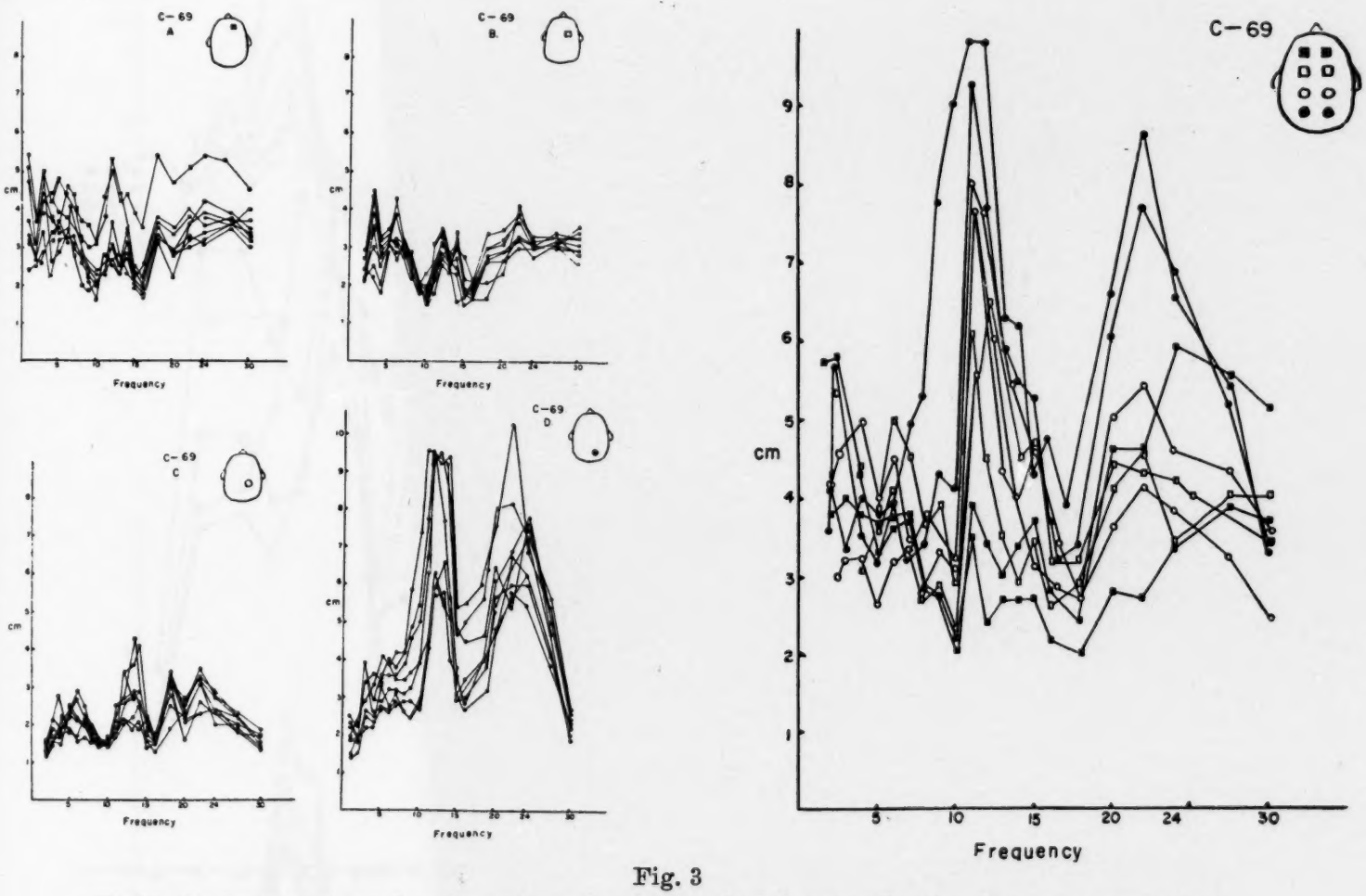


Fig. 3

Right, the frequency graphs of a patient showing marked dys-coordination between areas recording. There is wide spread of energy, poor alpha patterning and much fast activity. On the left, 8 successive epochs are superimposed from 4 areas from the same record. Dys-coordination among successive recordings from a single area is less marked than among the different areas.

base of the alpha peak was apt to be narrower.

These differences also appear in the graph averages. Thus, in figure 5, the first test of the 15 normal controls shows a high, narrow alpha peak, some theta, but little activity elsewhere. The average second test, taken one month later, has similar characteristics, except that alpha peak is lower, and there is slightly resulting average pattern still does not resemble that of either schizophrenic or non-psychotic patients (fig. 6).

Figure 5 (lower) shows the average frequency graph of the 15 patients who, because they were ultimately committed from the Crease Clinic to the Provincial Mental Hospital for long-term confinement, may be considered as the sickest of the patients examined.

The interval between EEG recordings in these 15 cases was often much longer than the one and two month intervals between recordings for the other graphs. This was due to the fact that many of these sickest patients had been sent home on parole or discharged, only to return after an interval to be placed in the more permanent hospital wards. All these patients, however, had their first examination while on a first admission to the Crease Clinic, areas; a wider alpha base; a higher total base line; and a wider spread between recording areas at the beta level than appear in test No. 1.

Figure 6 presents the graph averages of the other two groups, the "no treatment" group of non-psychotics (upper) and the schizophrenics having coma insulin treatment (lower). Seven of the former and 9 of the schizophrenics remained in hospital long

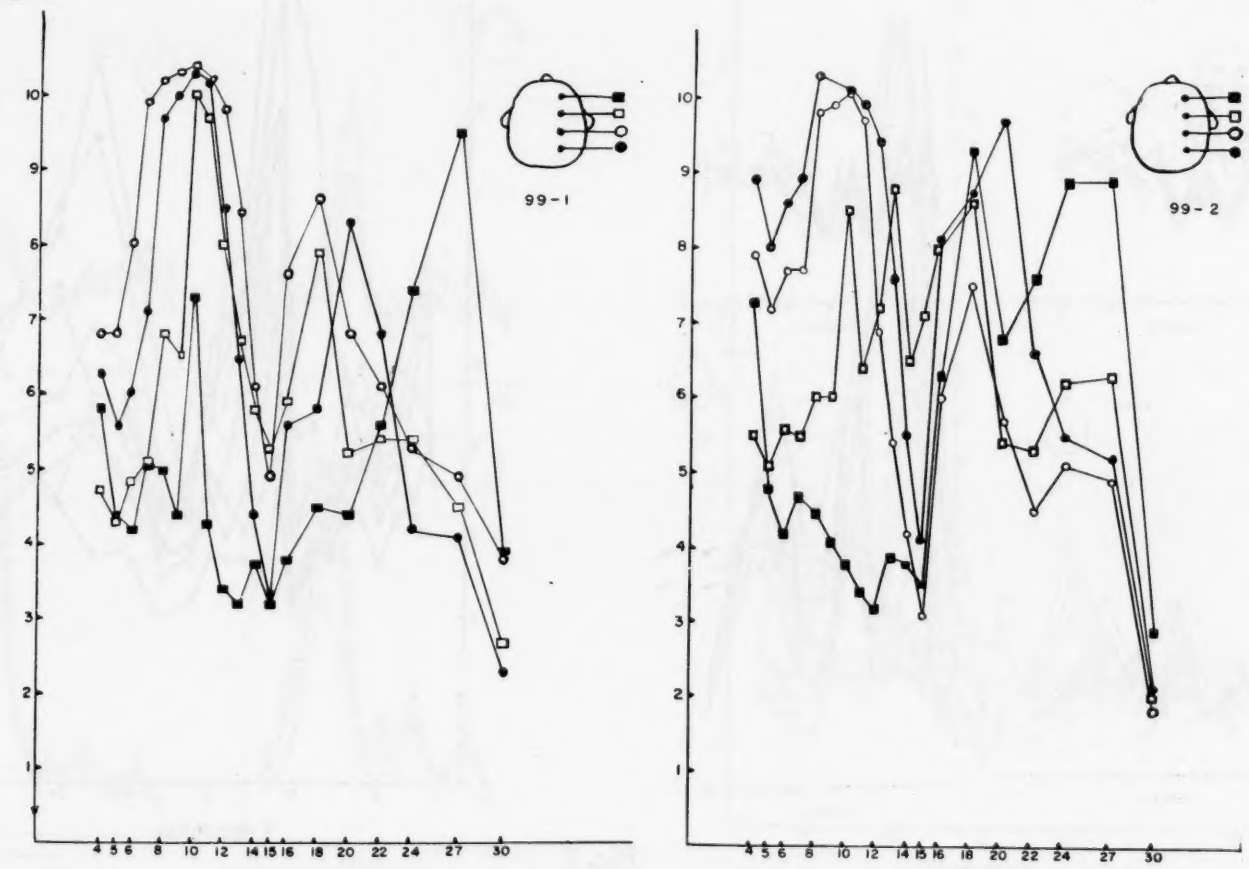


Fig. 4

Right, frequency graphs from the EEG shown in figure 1. (99). Although the record appears fairly stable, there is marked dys-coordination among recording areas as compared to that shown in figure 2 made from a similar record. Left, a second EEG from the same patient (99) showing little change.

when they were considered relatively lightly disabled from a relatively recent illness. All were, later, examined after being committed for a longer hospital term. All but three were schizophrenic. In contrast to the averages of the controls or to those of the other patients (fig. 6), this second graph is less "normal" than the first, for it contains a less sharp alpha peak; less synchrony between recording enough to have a third EEG test, administered during the third or fourth month of hospital stay. The schizophrenic graphs have the relatively wide spread, broad alpha base, and high total baseline characteristic for individuals within the group. But there is somewhat "better" coordination of lines and less beta activity at the third test, i.e., the second and third tests are more nearly like that of the

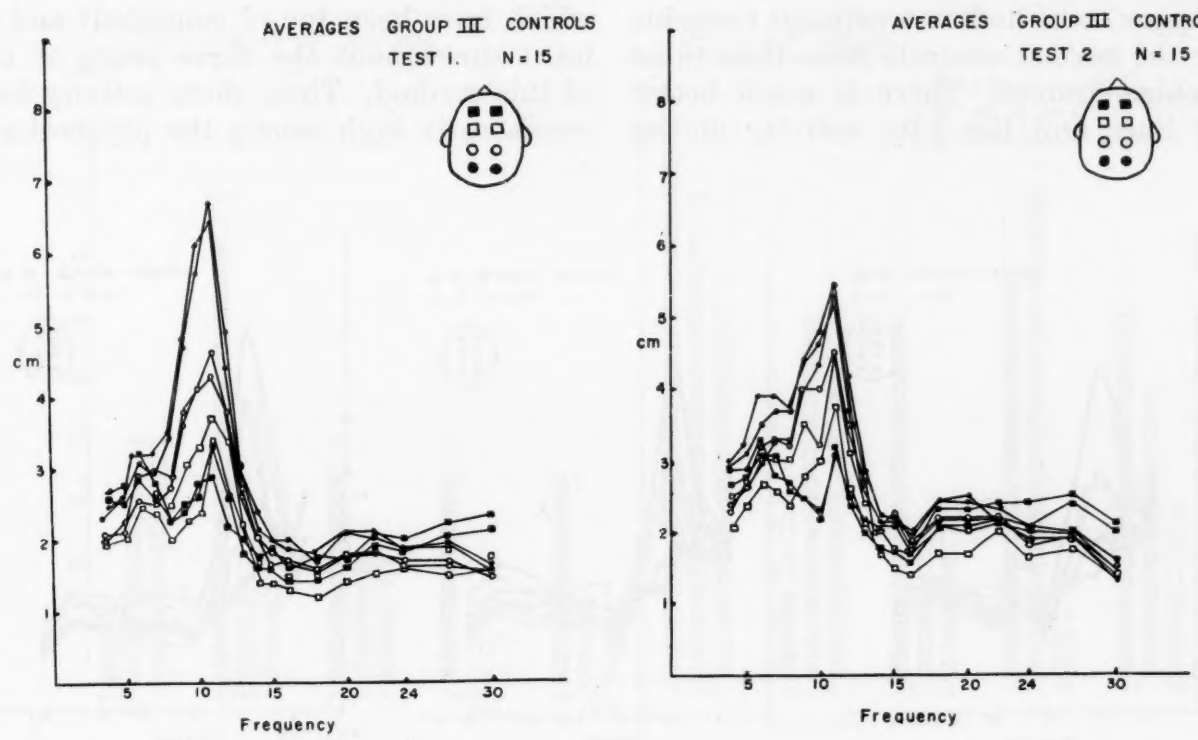


Fig. 5

EEG frequency graph averages made from 15 control subjects (upper) and 15 severely disturbed subjects, all committed to a chronic mental hospital.

normal group. The graphs of the non-psychotic group (upper) who had no treatment resemble those for the normal controls more than those of the schizophrenics. There is much better unity of lines and less beta activity among organization. Many points are illustrated here which have been found consistent and significant throughout the three years of our use of this method. Thus, theta activity has been consistently high among the psychotics where

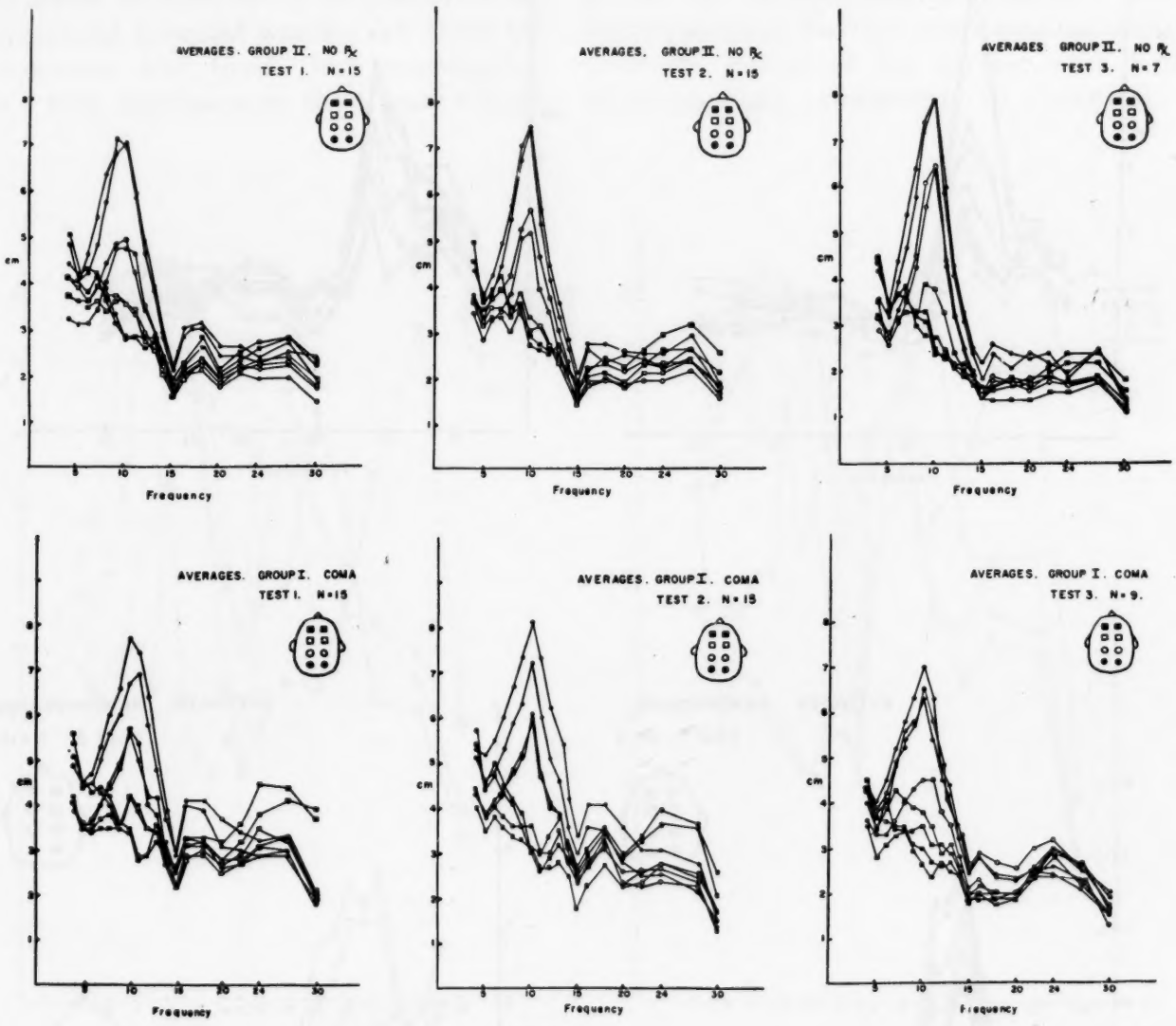
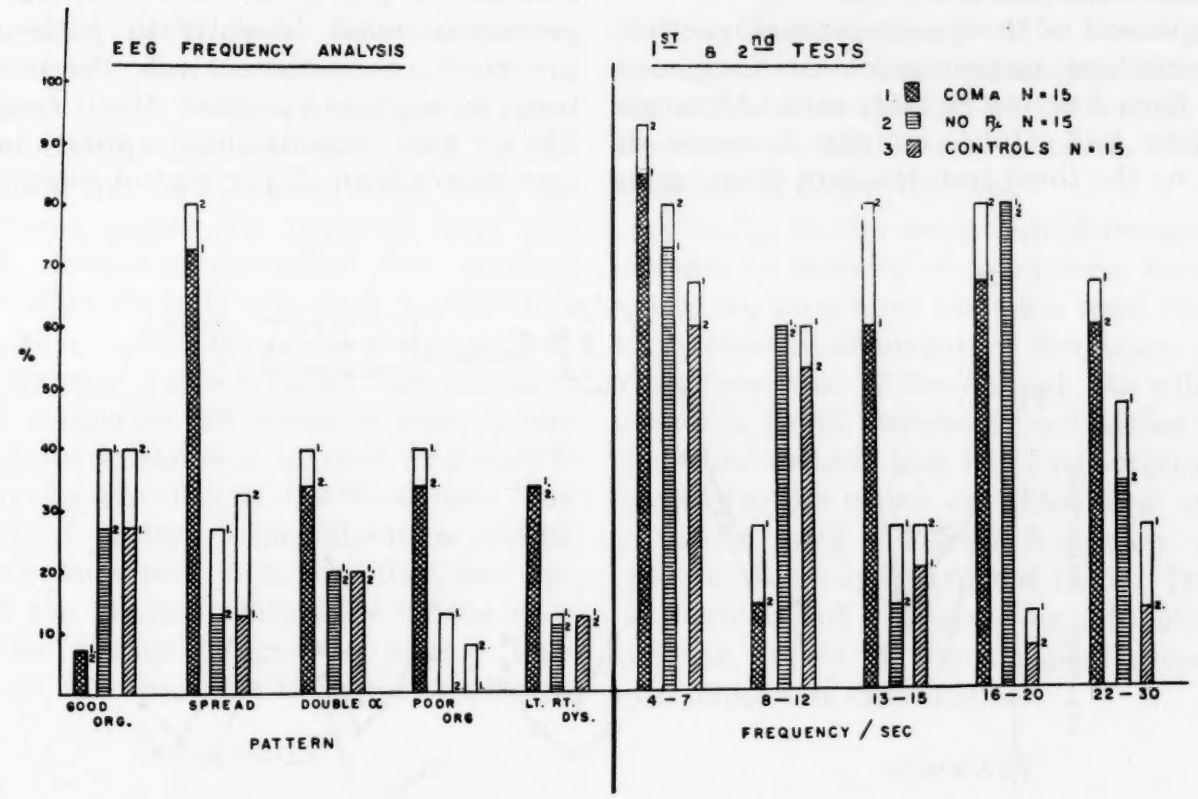


Fig. 6

EEG frequency graph averages from 15 patients having no specific treatment during hospitalization. These were relatively lightly disturbed and non-psychotic (upper) and 15 schizophrenic patients receiving coma insulin therapy between first and second tests (lower). The last graph in both instances more nearly resembles the control graph than does the first. These changes are more marked in the non-psychotic average group and were very strikingly so in individual cases within that category.

the recording areas from the third test than in the first.

Appraisal of the frequency patterns of each of these same groups of 15 subjects, by a different method, is presented in figure 7. Here, the per cent of activity present at the different frequencies is related to total pattern 13-15/sec. as well as 16-20/sec. wave forms are also common, but "good organization" is almost absent in this group. "Poor organization", very rare among the controls, "wide spread" of pattern, and "left-right" dyssynchrony are also significantly more prevalent among the schizophrenics. Both graphs,



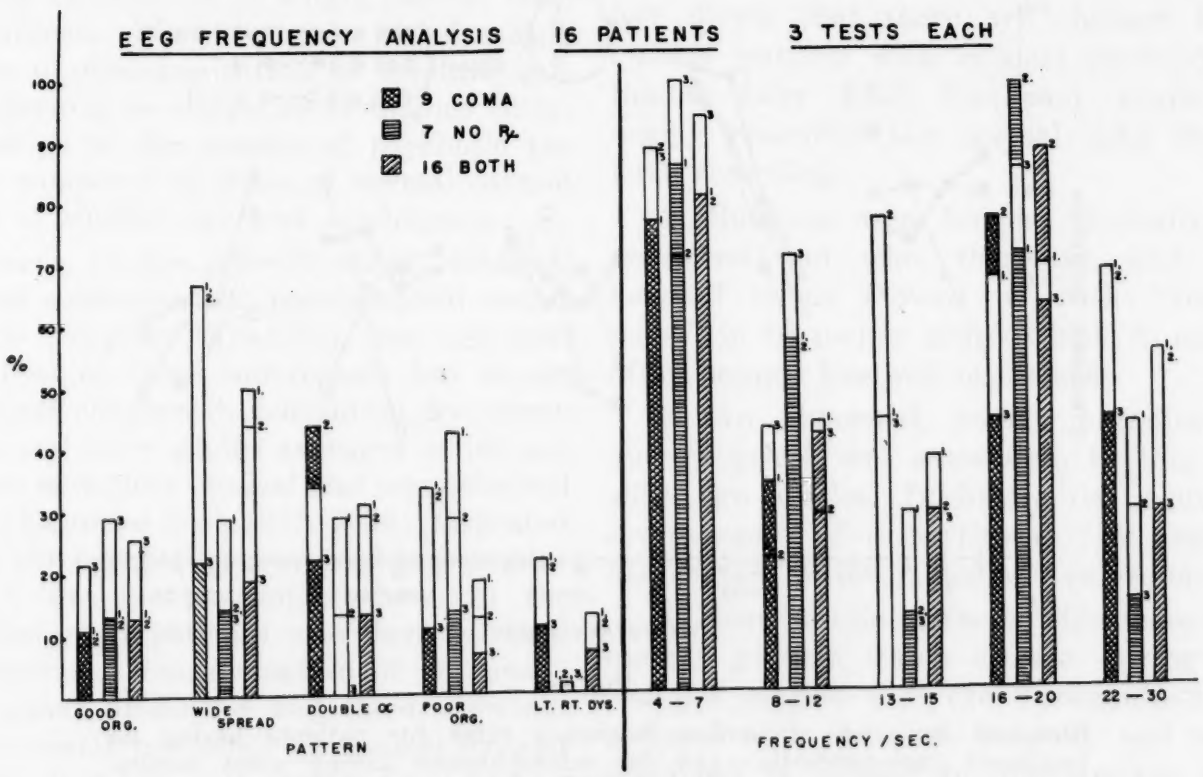


Fig. 7

Two figures showing the EEG frequency analysis according to criteria established from inspection of previous records. First test is numbered 1, and 2nd and 3rd (2 and 3) are at about one month intervals afterward. It will be seen that there is an increase in normal characteristics, particularly during the third test.

but in particular the lower one (fig. 7), with the comparison of three tests on each patient, show consistent improvement in frequency pattern from first test to later ones. Although both theta and alpha activity increase in amount by the third test, the beta frequencies become less prevalent. The most marked improvement, that is, shift to patterns more prevalent among the controls, lies in the pattern arrangement rather than frequencies. Thus, "good organization" appears in 25 per cent rather than 12 per cent of schizophrenics

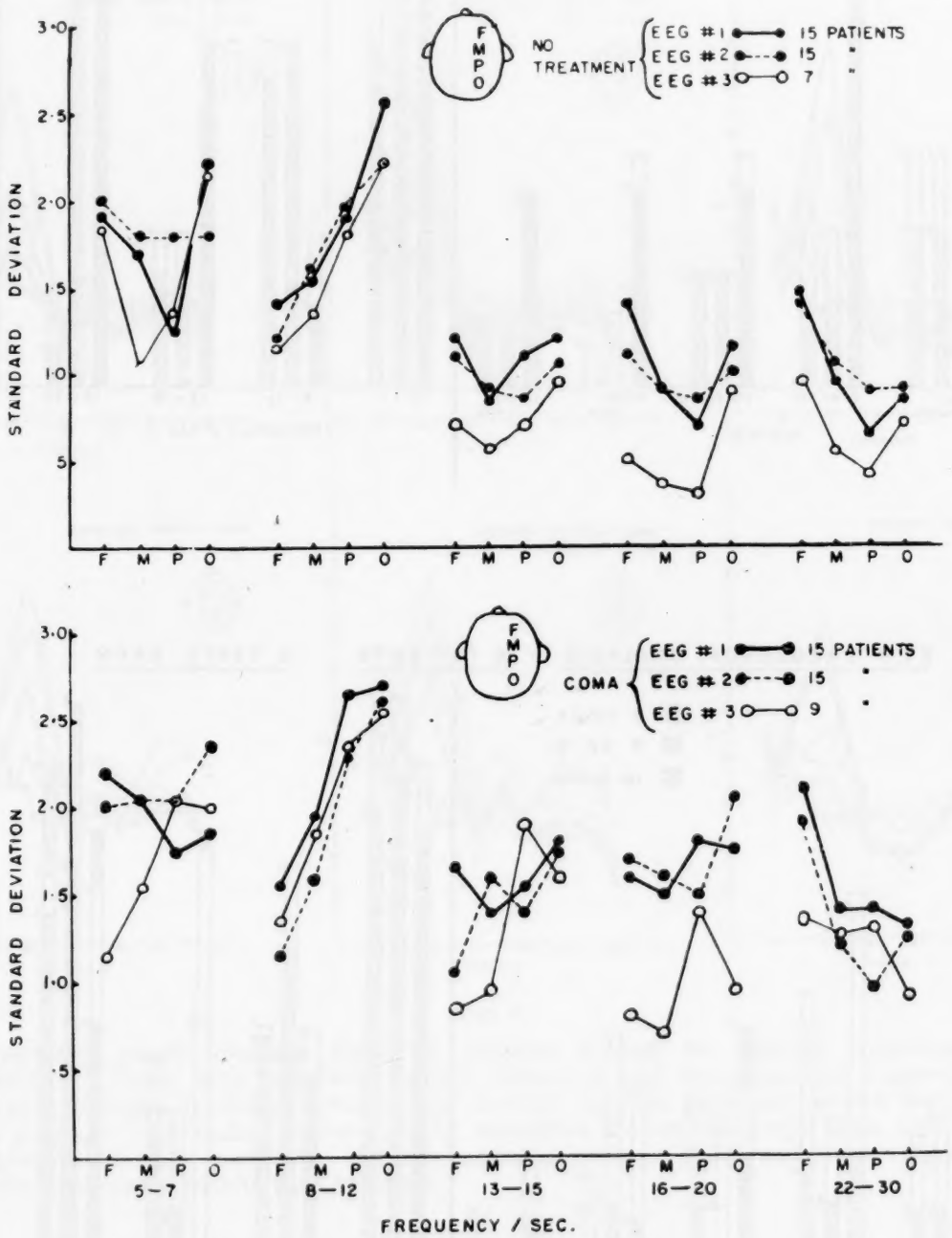


Fig. 8

Standard deviation of various frequency rates for patients having no treatment (non-psychotic) and for schizophrenics having coma insulin. Deviation among subjects falls at the last test in both groups, in both fast activity and theta. There is little change in alpha variability. The non-psychotic group show more consistent change. It is always greater in motor (M) and parietal (P) areas than in either frontal (F) or occipital (0).

by the third recording; "wide spread", "double alpha peak", and "poor organization" become far less frequent.

Finally, figure 8 shows similar changes when standard deviation is calculated for the three groups having two recordings each. In our previous paper we reported that the standard deviation estimated for another group of schizophrenics was much higher than that of either a normal control group or that of the inmates of a prison farm. The standard deviation estimated for repeated tests in our present patients shows a marked and significant drop by the time of the third test. The variability of pattern from patient to patient has thus become less, and, therefore, has approached the greater uniformity of the controls. This change is greatest among beta frequencies, but the alpha is almost unaltered.

DISCUSSION

In this longitudinal study of EEG frequency pattern relationships we have, therefore, confirmed many of the observations made previously on analyses of single records from single subjects. We have again found a high incidence of disorganization of cerebral cortical patterning as shown by frequency interrelationships in the graphs of psychotic patients as compared to those of normal control subjects of similar age and intelligence.

We have, in the present study, obtained additional evidence that psychological status relates to frequency pattern, for repeated examination of these individuals has shown longitudinal changes in individual frequency patterns and their group averages which are coincident with their clinical and psychological changes (Kennard *et al.* 1955, 1956). Repeated EEGs in the psychotic group, and to a greater extent in the non-psychotics show, in the lightly disturbed patients who were released from hospital, a reorganization of frequency pattern which at second and third examination more nearly resembles the normal pattern than at the first test. It is obvious from figures 6 and 7 that this change is more marked after the second month in hospital than after the first. Unfortunately, this finding only appeared after many recordings had been made at the shorter interval. Also, because of the type patient we were examining, many were not available at the end of the second month. However, future re-examinations should be made at the longer interval.

Finally, in the one group showing clinical increase in severity of symptoms, those committed for long term custodial care, there was an increase in distortion of frequency pattern away from that of the normal. As will be reported in detail elsewhere, correlation of psychological criteria and EEG patterning showed two factors which are those most strongly correlated with distorted frequency pattern (Schwartzman and Kennard 1956). These are the acuteness of the psychological disturbance and the degree of psychological dissociation with immediate environment.

SUMMARY

1. A longitudinal study of EEG frequency patterns of mental hospital patients as compared to those of a matched control group has shown that there are changes in frequency pattern with clinical recovery such that a later EEG frequency graph more nearly resembles the normal than does the first recording.

2. Subjects who became clinically more disturbed and who, therefore, had longer hospital terms showed no such "improvement" in frequency graph which, in contrast, often became less well organized.

3. An abnormal, poorly organized frequency graph was associated, in this series, with two clinical findings; (*a*) acute and severe onset of disturbance; (*b*) degree of dissociation with immediate environment.

4. Examination of these differences in frequency pattern which appear during clinic changes suggest that the disorganization associated with the more severely and acutely disturbed is related to organization among various cortical areas rather than to variability of pattern as recorded successively from a single area.

The authors wish to thank Dr. William P. Fister for his cooperation. Most of the EEG recordings were done in his Laboratory. His assistance and that of his staff over a three year period has been greatly appreciated.

REFERENCES

KENNARD, M. A., RABINOVITCH, M. S. and FISTER, W. P. The use of frequency analysis in the interpretation of the EEGs of patients with psychological disorders. *EEG Clin. Neurophysiol.*, **1955**, *7*: 29-38.

KENNARD, M. A., RABINOVICH, M. S., SCHWARTZMAN, A. E. and FISTER, W. P. Factor of aggression as related to the electroencephalogram. *Dis. Nerv. System*, **1956**, *17*: 3-7.

RABINOVITCH, M. S., KENNARD, M. A. and FISTER, W. P. Personality correlates of electroencephalographic patterns: Rorschach findings. *Canad. J. Psychol.*, **1955**, *9*: 29-41.

SCHWARTZMAN, A. E. and KENNARD, M. A. Assessment of psychiatric patients by psychological tests and the electroencephalogram (In preparation, 1956).

Reference: KENNARD, M. A. and SCHWARTZMAN, A. E. A longitudinal study of electroencephalographic frequency patterns in mental hospital patients and normal controls. *EEG Clin. Neurophysiol.*, **1957**, *9*: 263-274.

PRINTED IN CANADA

ELECTROENCEPHALOGRAM WITH CHROMOPHOBE ADENOMATA AND RATHKÉ POUCH CYSTS: MODIFICATION BY ASSOCIATED METABOLIC DISORDER

F. Boselli, B.A. and A. A. Jefferson, M.D.
Departments of Electroencephalography and of Neurosurgery,
The Radcliffe Infirmary, Oxford, England

(Received for publication: September 26, 1956)

INTRODUCTION

It would be generally agreed that tumours lying in and around the third ventricle give rise to a theta rhythm which is usually well defined and bilateral (e.g. Cobb 1950). However, there is a surprising absence of publications devoted to the description of the electroencephalogram (EEG) in an important group of lesions which affect this region — namely many of the pituitary adenomata and Rathké pouch cysts. In 1946 Lennox and Brody described the findings in a very small group of "pituitary tumours" and, using the evidence of these cases in combination with other experience, concluded that 4-6 c/sec. waves were associated with lesions of the hypothalamus. A description of the findings in 6 further cases of pituitary disease is to be found among the 90 patients with lesions of the base of the brain described by Fauré, Jasper and Henderson (1948). Thus, when Tönnis, Steinmann and Krenkel (1953) recently published an article on the EEG in 44 cases of parasellar and intrasellar lesions they were describing experience derived for the first time from a fairly large group of such patients. They suggested that metabolic factors, rather than pressure by tumour upon the hypothalamus, were responsible for the appearance of theta rhythm in the records of these patients. This statement was in direct contrast to the earlier view of Baudouin, Puech, Fischgold and Lerique-Koechlin (1946) who had only observed disorders of the EEG when a pituitary tumour lay above the diaphragma sellae and therefore might impinge upon the floor of the third ventricle.

The present paper is concerned with the electroencephalographic findings in 59 patients with a pituitary chromophobe adenoma and in 17 patients with a Rathké pouch cyst. In many cases serial records have been obtained, and the influence upon the EEG of metabolic disorders secondary to the pituitary disease has been studied.

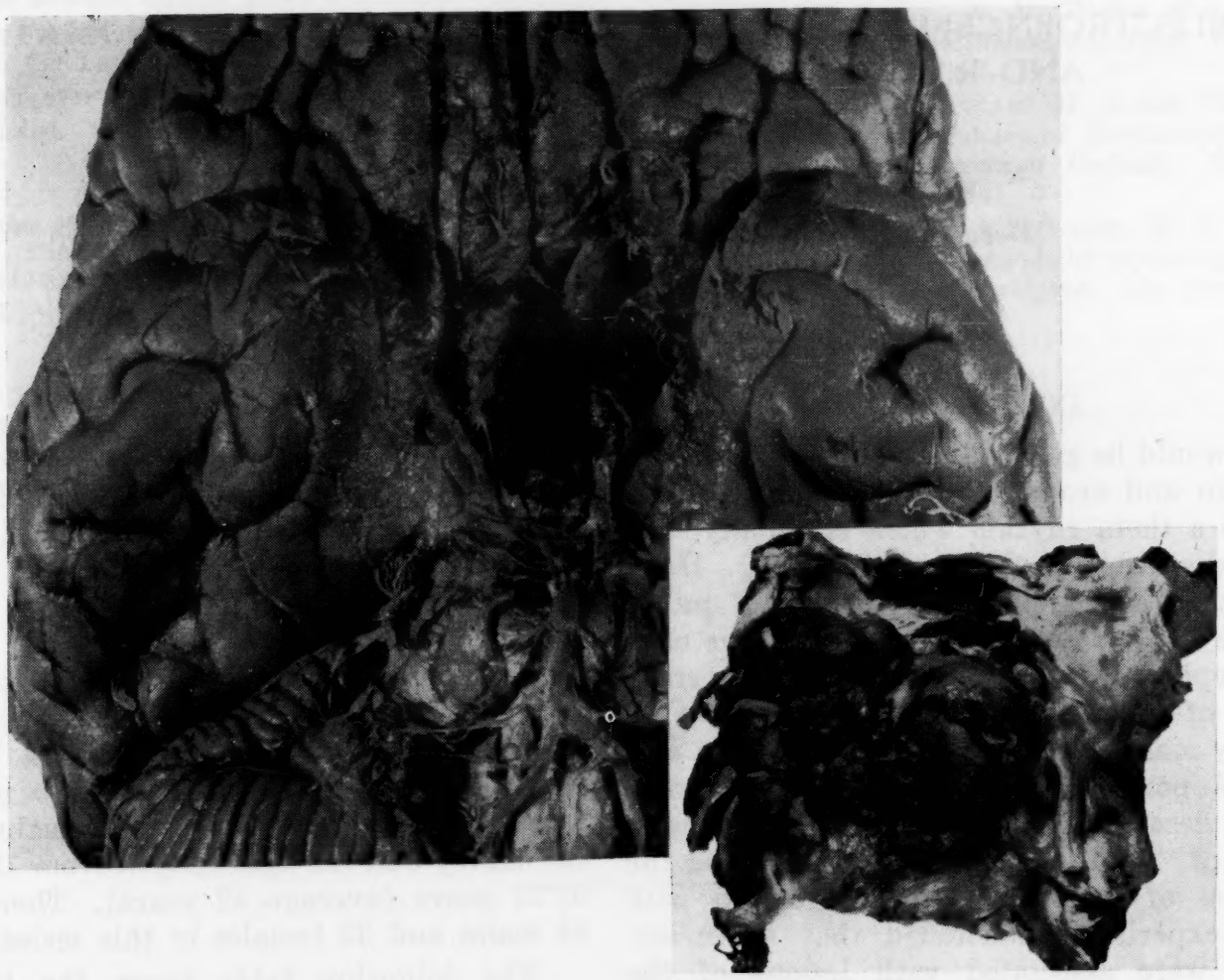
MATERIAL

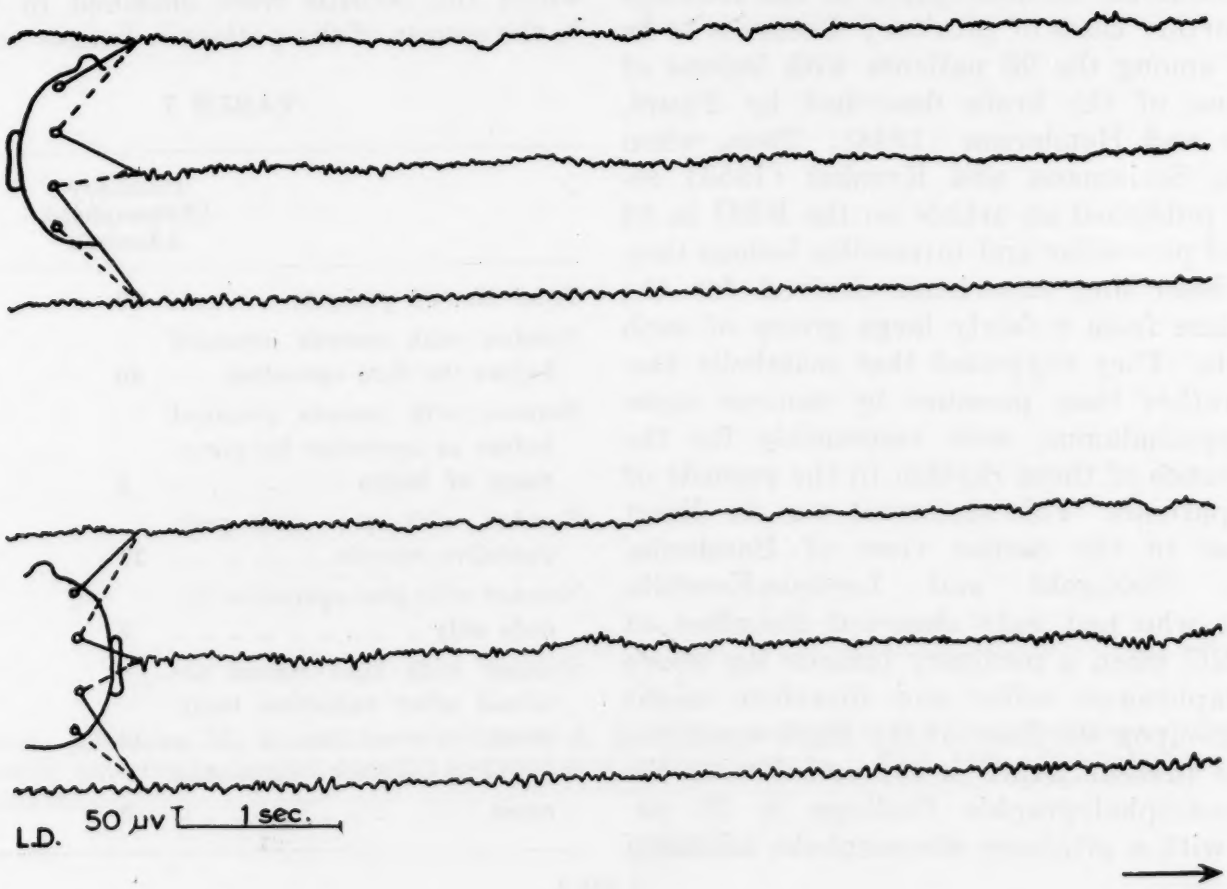
A total of 102 records from 59 patients with a chromophobe pituitary adenoma and 32 records from 17 patients with a Rathké pouch cyst have been reviewed. No patients below the age of 18 years were included in the survey and the ages ranged from 18 years to 71 years (average 42 years). There were 44 males and 32 females in this series.

The following table shows the time at which the records were obtained in relation to the course of the patient's disease (table I).

TABLE I

	Pituitary Chromophobe Adenoma	Rathké Pouch Cyst
Total No. of patients	59	17
Number with records obtained before the first operation	46	15
Number with records obtained before an operation for recurrence of lesion	2	1
Number with pre- and post-operative records	17	8
Number with post-operative records only	8	2
Number with first record obtained after radiation treatment	12	0
Number of surgically unverified cases	5	2




L.D.
50 μv
1 sec.

Of the patients with a pituitary chromophobe adenoma 4 had papilloedema and 2 others, although not showing papilloedema, had evidence of raised intracranial pressure at operation.

METHOD

For one record dating from 1942 a cathode ray oscillograph was used; records from 1942-1949 were taken with a 3 channel Grass ink-writing electroencephalograph and thereafter with a 6 channel Ediswan instrument. Recording was bipolar throughout.

Description of the record with pituitary chromophobe adenoma

The most distinctive feature in the bulk of the records was a clear theta rhythm (4-7 c/sec.); in 16 this was a 6 c/sec. rhythm of small amount and it was confined to the anterior temporal and to the frontal areas. Often this rhythm was only seen in the transverse leads after overbreathing. In 22 records a well-defined theta rhythm was present, usually predominating in the anterior leads and of greater amplitude than the occipital alpha rhythm. Many of this group also had random slower waves, sharp elements and pronounced fast activity. In 36 a bilateral 5-7 c/sec. rhythm was the main component of the record. It was almost continuous, of fair regularity and of greatest amplitude and slowest frequency over the anterior part of the head. This rhythm was usually poorly affected by sensory stimuli. Most of this group also had slower waves and over half had fast activity. There were 10 normal or border-line normal records. Nine records were of generally low voltage, often with pronounced fast activity. In addition to these, 6 records did not fit into any of the above mentioned categories, but in each instance there was evidence of raised intracranial pressure. One of these patients had a large lateral extension of his pituitary adenoma and the clinical, angiographic and electrical signs of this case were all those of a temporal lobe tumour. Finally, there were 3 records in which generalized delta waves predominated; one of the patients was in coma, and the occurrence of the delta waves in the other 2 patients will be discussed below (see fig. 2).

In the group of 36 patients where the theta rhythm formed the main component the average duration of visual symptoms was 5 years. If earlier related symptoms, some of them metabolic (e.g. infrequent shaving in the male, amenorrhoea in the female), are taken into account, the average duration of the illness was 16 years. For all the lesser affected groups the average duration of visual symptoms was between 1½-3½ years and the estimated maximum duration of the disease was only 9 years.

Slight asymmetries of amplitude and amount of theta rhythm were common, but asymmetries of frequency only occurred in 15 patients. In 2 the theta activity was unilateral, in 12 it was slower on one side than on the other, and in one the asymmetry was confined to the alpha rhythm. Among the patients with definite asymmetry of electrical activity the more abnormal side corresponded on 9 occasions to the side on which the tumour had compressed the visual pathways more severely; in 3 patients the reverse occurred. In 2 other patients the asymmetry of the theta and alpha rhythms was associated with a delta wave focus, and in both of these there was proof of an extensive extrasellar extension of the tumour in the affected hemisphere. One patient with a huge suprasellar extension producing hydrocephalus had bifrontal rhythmic delta waves.

The effect of overbreathing was examined on 63 occasions; gross instability of the record induced by overbreathing was only seen when the record was initially severely abnormal. However, a severely abnormal resting record showed either no change or only a mild change on 8 occasions.

Fig. 1

Above. Base of brain to show indentation caused by pressure of suprasellar tumour. Inset shows tumour viewed from above.

Record almost within normal limits; the only doubtful features of the record as a whole were the presence of low voltage irregular fast activity and of minimal theta waves.

Deflection for 50 μV. is of 4 mm. in figure 1 and 9 and of 7 mm. in all others.

In table II differing grades of electrical abnormality are tabulated against estimates of tumour size and degree of endocrine deficiency. If attention be confined to the "more severely abnormal" records it can be seen that these were distributed almost equally between "small", "medium" and "large" tumours, but were unequally distributed between the grades of endocrine abnormality; the vast majority of "more severely abnormal records" occurred in patients with "moderate" or "severe" endocrine disorders. One patient classified as having a severe endocrine deficiency had a low voltage record, but the remaining 7 patients with severe endocrine deficiency had either a theta-dominant or a delta-dominant record. In contrast to this, 5 patients with large tumours had records which ranged between normal to moderately disturbed. Indeed, one man of 52 who had only a mild degree of endocrine failure had a large tumour which was found after death to be indenting the base of his brain (fig. 1); but the record was almost within normal limits.

TABLE II

THE CORRELATION BETWEEN EEG, TUMOUR SIZE AND ENDOCRINE ABNORMALITY

EEG	*Tumour size*			*Degree of endocrine disturbance*			
	Small	Moderate	Large	Minimal	Slight	Moderate	Severe
Normal, borderline and mildly abnormal	13	6	2	10	8	2	1
Moderately abnormal	6	4	3	7	3	3	0
More severely abnormal	5	5	7	1	1	8	7

These figures are derived only from those cases in which the size of the lesion was verified surgically or radiologically shortly after the record was obtained.

The findings set out in table II confirm the view that in patients with a pituitary chromophobe adenoma the possible effects of metabolic changes upon the electrical activity of the brain have had insufficient attention paid to them. The following case of a pituitary chromophobe adenoma with no significant suprasellar extension illustrates the profound effects which metabolic abnormalities may produce.

Case 1. Male, aged 63 (R.I. 179989/55) was admitted to the Radcliffe Infirmary on 23.9.55. He was confused, demented and disorientated and had reached this state in the course of an illness, the acute phase of which had begun 5 weeks earlier. Although his fundi appeared slightly pale, there was no field defect to confrontation and later, when he became cooperative, it was shown that there was a partial hemianopia, demonstrable only with small objects, in one eye alone. On 1.10.55 a lumbar air encephalogram was performed, and this showed no sign of suprasellar extension of the tumour. On 29.9.55, at a time when he was totally confused, the EEG (fig. 2a) showed generalized delta waves. Because this patient had clinical features (and also an abnormal water metabolism) suggestive of anterior pituitary hypofunction, treatment with cortisone, 25 mg. t.d.s., was begun on 27.9.55; to this were added a small dose of thyroid extract and some methyl testosterone. The next record was obtained on 5.10.55, at which time the patient was considerably improved. The EEG now (fig. 2b) showed a great decrease in the numbers and amplitude of the delta waves. The record was still uninfluenced by engaging him in conversation, but there was a slight reaction to eye-opening. Five days later, on 10.10.55, a slow alpha rhythm had begun to emerge (fig. 2c). His clinical state continued to improve so that by 12.10.55, when he commenced a course of radiation treatment directed to his pituitary tumour, he ended a period of amnesia which dated from 21.8.55. By 9.11.55. he was able to walk round the ward with assistance and he was alert and orientated, although his mentality was still not quite normal. An EEG obtained two days later (fig. 2d) showed a well-defined alpha rhythm which was now faster (8-9 c/sec.) and there was no appreciable theta rhythm.

This patient's electroencephalographic abnormalities receded from the moment of the commencement of hormone replacement therapy. Of the hormones prescribed it is likely that cortisone was the relevant agent, for a somewhat comparable improvement in the EEG was recently observed in a patient with pure adrenal cortical failure. This patient was admitted to the Radcliffe Infirmary, under the care of Dr. A. M. Cooke, and we are indebted to him for permission to describe the clinical details.

Case 2. Male, aged 32 (R.I. 198915/54) had developed neurological symptoms and signs and subsequently went into an adrenal "crisis" and appeared moribund with profound circulatory failure and stupor. Immediate and vigorous treatment with cortisone and related agents was successful, and the clinical response was dramatic. On 28.5.55, 24 hours from the beginning of the treatment, the first EEG was obtained. The patient was co-operative; he would answer rationally, but he was a little apathetic. This record (fig. 3a) was in general similar to that of figure 2a except for the absence of any fast activity. In this case there can be no doubt that the generalized delta waves were not correlated with the patient's level of consciousness, as, in contrast to case 1, he was not drowsy nor did he appear confused. By 31.5.55, when the patient was feeling mentally and physically almost normal, the slow waves in the EEG had very nearly disappeared (fig. 3b). On 14.6.55, at which time the patient's personality and mentality had been regarded as normal for some 12 days, the EEG still showed slight abnormalities (fig. 3c). There was still some diffuse theta activity but the alpha rhythm had now returned at a rate of 8 c/sec.

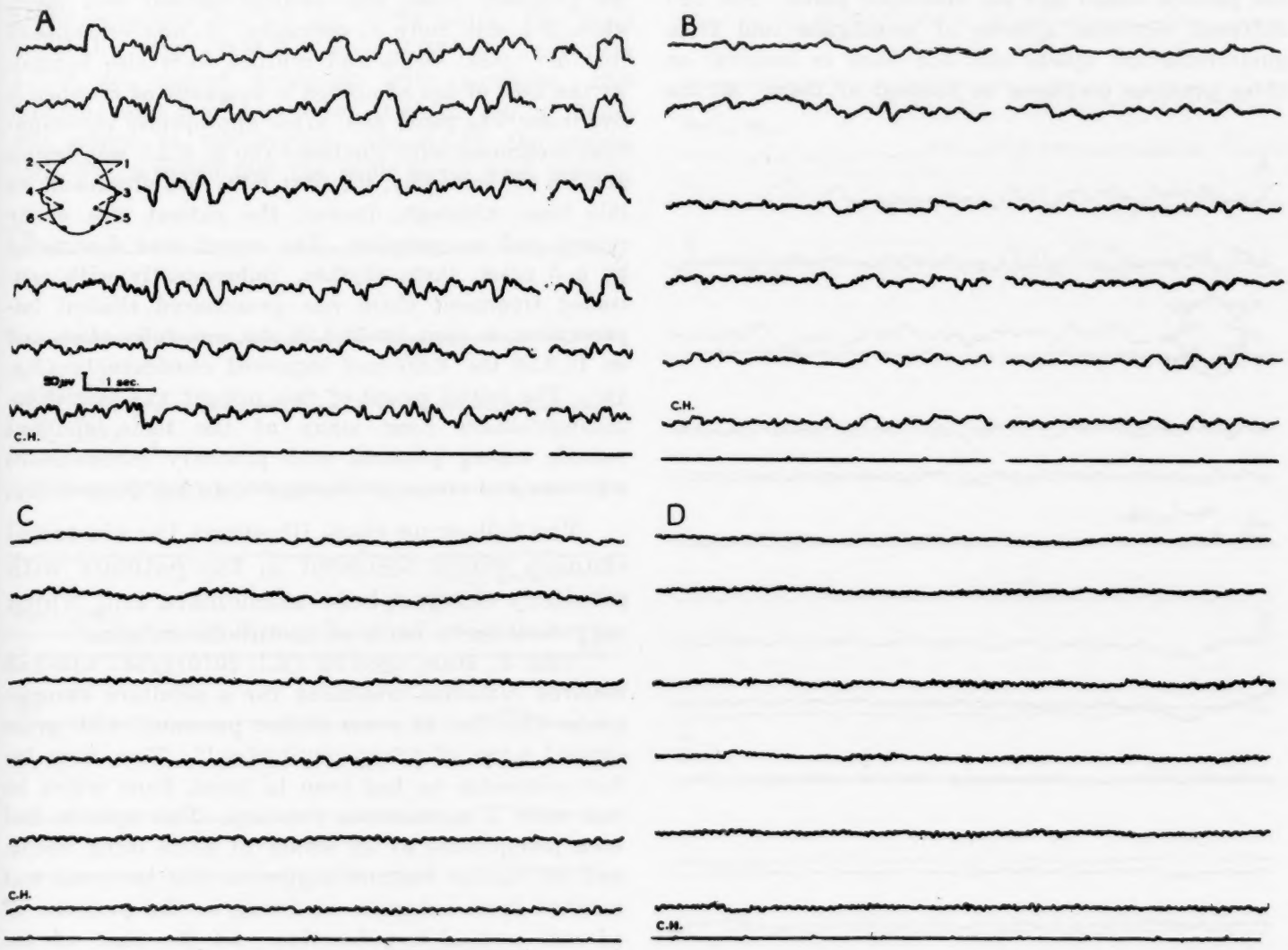


Fig. 2

Case 1. Serial EEG.

A. Obtained on 29.9.55. Note generalized delta waves of greatest amplitude frontally. These were usually bilaterally synchronous and occurred on a background of irregular low voltage fast activity and 4-7 c/sec. waves. The record was unaltered whether the patient held his eyes open or closed. Overbreathing could not be attempted.

B. 5.10.55. After 9 days of hormonal treatment. The record shows considerable improvement.

C. 10.10.55. There is a slow alpha rhythm (7-8 c/sec.). (This responded well to eye-opening.)

D. 11.11.55. Note well-defined alpha rhythm at 8-9 c/sec., no appreciable theta rhythm and fast activity in the fronto-parietal areas. Overbreathing caused little change. Record was within normal limits for the age of the patient (63 years).

Case 3. Female, aged 62 (R.I. 24666/44) was ad-

mitted to the Radcliffe Infirmary on 20.3.56 under the care of Dr. P. C. Mallam, to whom we are grateful for permission to record the following clinical details. The significant item in the past history of this patient was that 36 years earlier, at the age of 26, she had suffered post-partum haemorrhage associated with a retained placenta. From that time on her periods ceased and she developed pallor. She had suffered recurrent attacks of meningism and from gastrointestinal upsets and had been in hospital on three previous occasions on account of them. At the time of the most recent admission she was stuporose and restless, with cachexia and extreme pallor of the skin but not of the mucous membranes. The axillary hair was very sparse and the pubic hair was absent. Apart from the stupor and the neck stiffness there were no abnormal neurological signs. Her blood pressure was 120/80. X-rays of her skull showed that the pituitary fossa was entirely normal and later, when she was fully co-operative, it was established that her visual fields and acuities were also normal. At the time of her admission a diagnosis of Sheehan's Syndrome was made and, after appropriate investigation, treatment with cortisone (50 g. b.d.) was begun and, on the same day, the first EEG was obtained. At this time, although drowsy, the patient was easily roused and co-operative. The record was dominated by a 5 c/sec. theta rhythm. Subsequently with continued treatment there was pronounced clinical improvement so that by 29.4.56 she was fully alert and on 10.5.56 the EEG had improved considerably (fig. 4b). The initial record of this patient was almost indistinguishable from many of the theta-dominant records among patients with pituitary chromophobe adenoma and visual involvement (cf. fig. 5a and 8b).

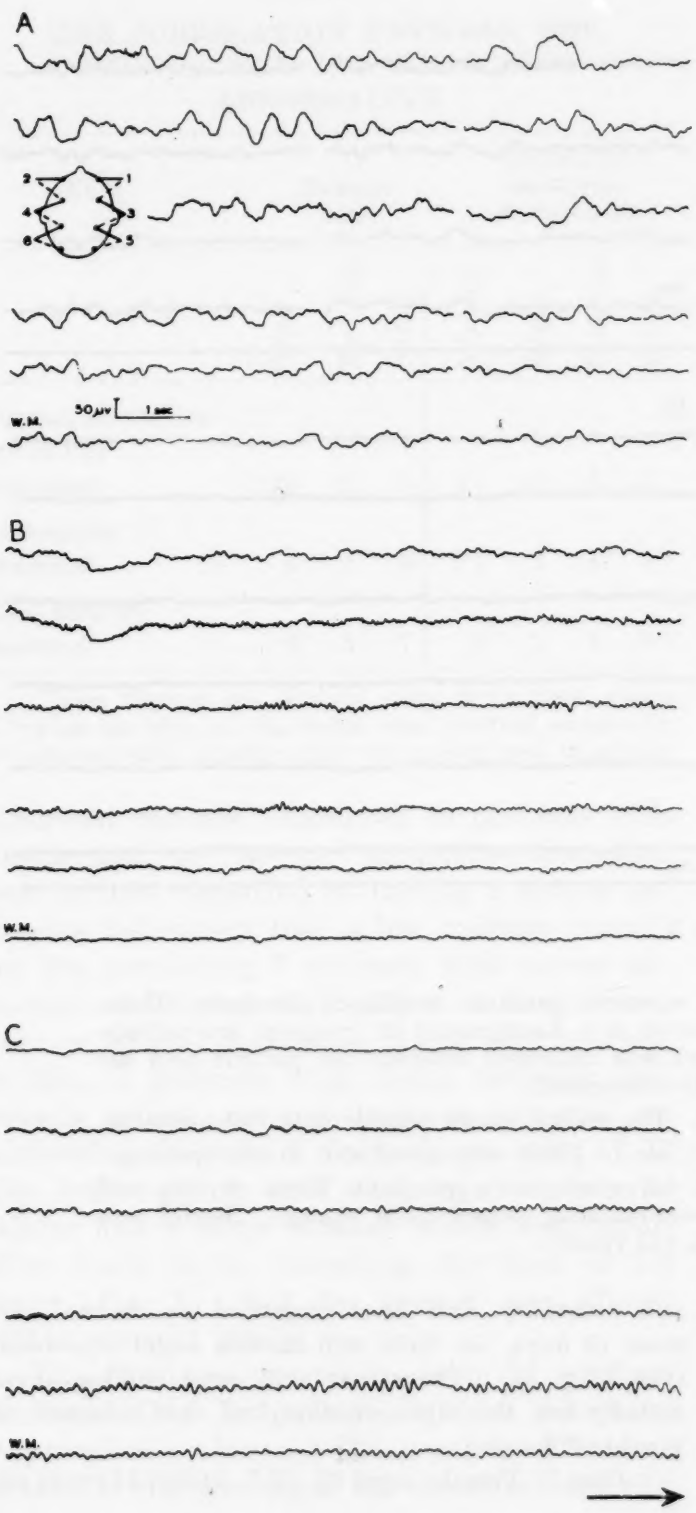


Fig. 3

Case 2. Serial EEG's.

A. 28.5.55. After only 24 hours' treatment with cortisone. Note generalized delta waves; in the main bilaterally synchronous. Little or no response to eye-opening. Overbreathing not attempted.

B. 31.5.55. Slow waves now nearly absent in the resting record, though returning on overbreathing. A few 4 c/sec. waves had appeared and faster activity mainly at 14 c/sec. was pronounced in the fronto-parietal areas. No appreciable alpha rhythm.

C. 14.6.55. Diffuse theta activity still present, but alpha rhythm now returned at 8 c/sec. and showed a normal response to eye-opening. There was no longer any trace of 14 c/sec. activity. No response to overbreathing.

The following cases illustrate the electrical changes which occurred in the patients with pituitary chromophobe adenomata and which may well have been of metabolic origin.

Case 4. Male, aged 52 (R.I. 207012/55) who had received radiation treatment for a pituitary chromophobe adenoma 15 years earlier presented with gross clinical signs of ''hypopituitarism''. Five days before admission he had been in coma, from which he had made a spontaneous recovery. This episode had been precipitated by an attack of acute otitis media, and the clinical features suggested that the coma had resulted from infection occurring in the presence of adrenal cortical hypofunction. At the time of the first record, 20.4.55, this patient was drowsy, rather

querulous and not very co-operative. The feature of the record (fig. 5a) was a bilateral moderately high voltage 5 c/sec. rhythm. There was good evidence of adrenal cortical hypofunction from the Thorn test and also from the water loading test (Oleesky and Stanbury 1951) carried out without and with preceding cortisone (respectively 8 per cent and 180 per cent of the "water load" excreted). His 17-ketosteroid excretion was 0.2 mg. in 24 hours. His basal metabolic rate (B.M.R.) was —39 per cent. On 1.5.55. he started treatment with cortisone, 12.5 mg/b.d., and two days later thyroid, 1½ g. daily, was added to the regime. On 5.5.55 the record (fig. 5b) revealed that the theta waves were reduced

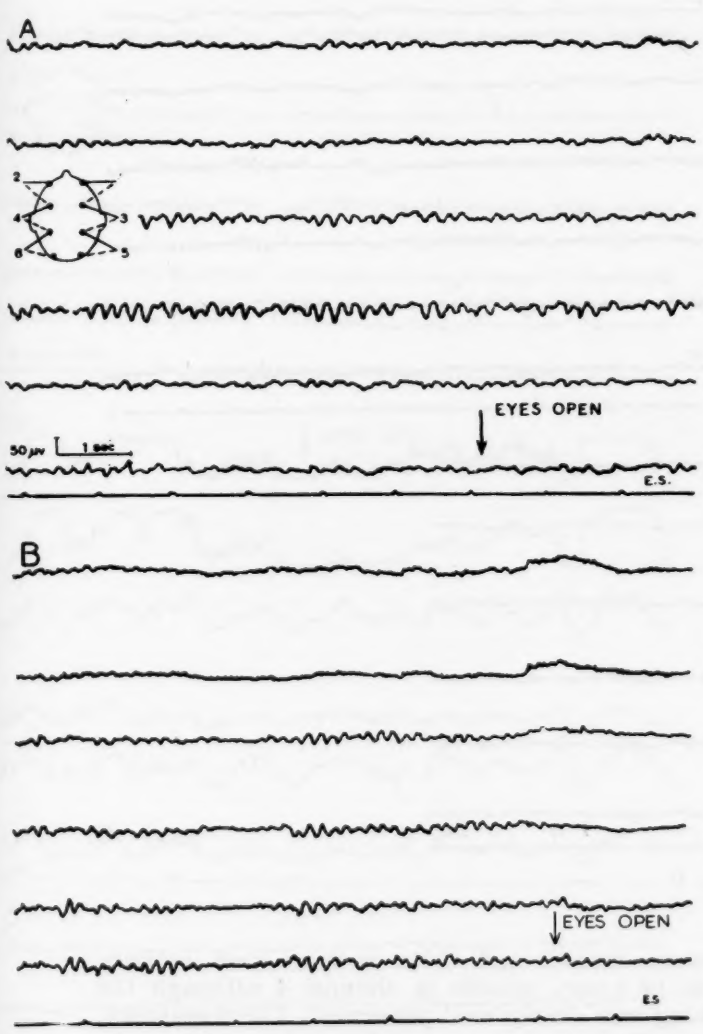
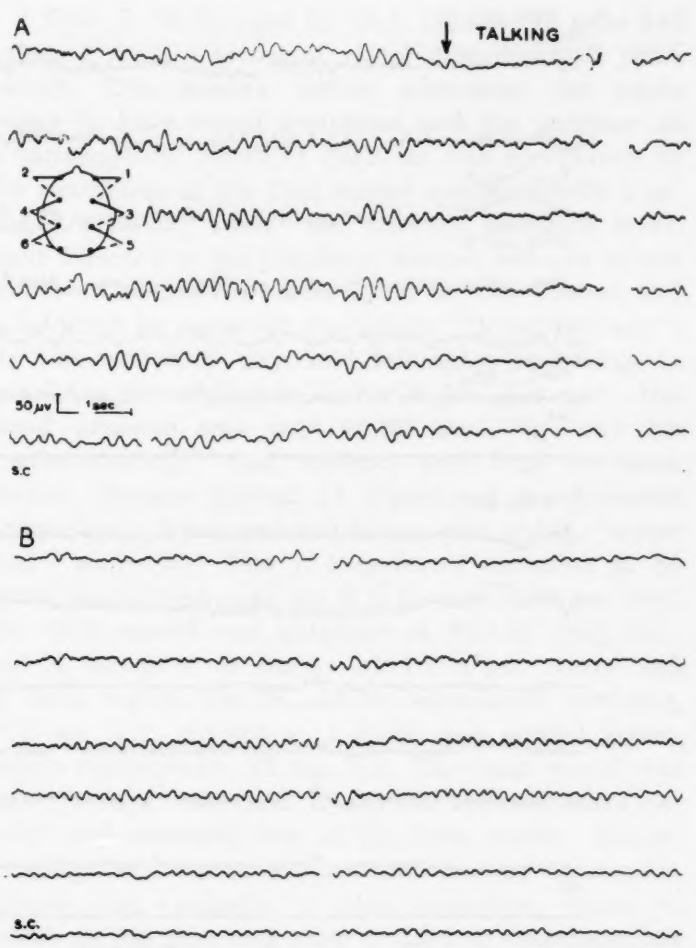


Fig. 4

Case 3. Serial EEG's.

A. 24.3.56. Generalized 5 c/sec. theta activity of moderately high amplitude. There are many 2 per sec. delta waves. Activity is not inhibited by eye-opening though slightly reduced when patient was talking (last second of tracing).

B. 10.5.56. After 7 weeks' treatment with cortisone. Basic rhythm is 1 c/sec. faster and nearer normal in distribution. Delta waves were infrequent and barely increased by over-breathing. Note response to eye-opening.



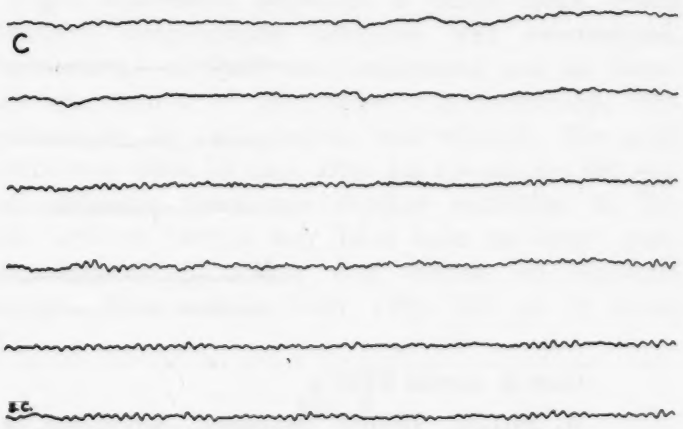


Fig. 5

Case 4. Serial EEG's.

A. 20.4.55. Bilateral high voltage 5 c/sec. rhythm present in all areas, but of greatest amplitude anteriorly. Relative absence of fast activity. Arrow shows effect of attention.

B. 5.5.55. After 4 days' hormonal treatment; theta waves reduced in amplitude and increased in rate to 6 c/sec. Effect of eye-opening more pronounced.

C. 22.6.55. Theta rhythm further reduced; dominant frequency 8 c/sec. Occasional 7 c/sec. runs still seen in the fronto-temporal area.
Reaction to eye-opening almost normal.
Overbreathing produced little effect but this was poorly performed on each occasion.

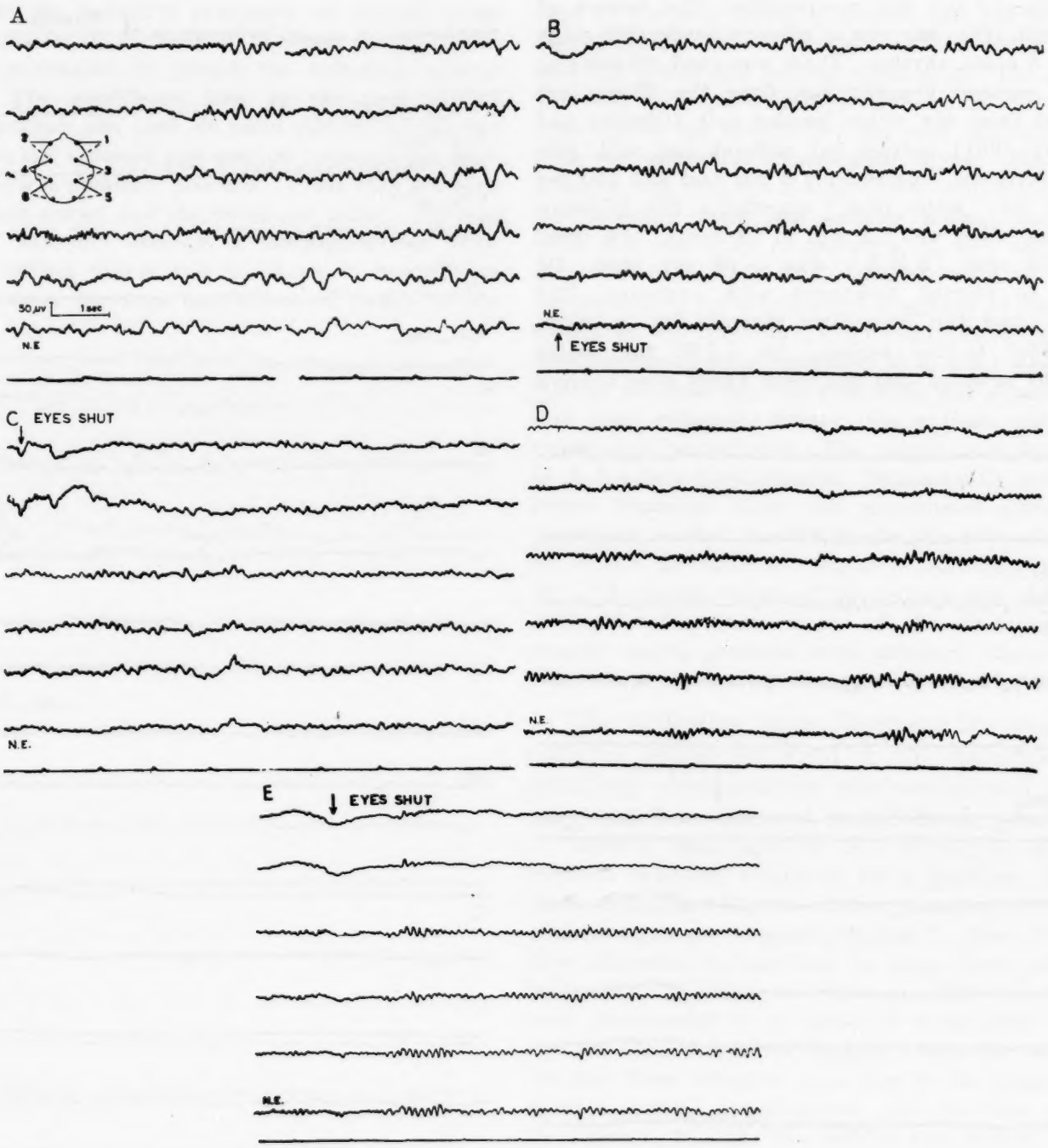


Fig. 6

Case 5. Serial EEG's.

A. 24.1.55. Before treatment. 4-5 c/sec. waves in bursts, and delta waves. Fast activity was present in the fronto-parietal areas; note 14 c/sec. spindle in channel 4 although the patient was awake. The response to eye-opening was fairly well preserved. Overbreathing, even though poorly performed, produced generalized high voltage slow waves after only 40 sec.

B. 29.1.55. After 3 days' hormonal treatment. Number and amplitude of delta waves is reduced; theta wave frequency increased to 5-6 c/sec. Fast activity was less evident. The record was less sensitive to overbreathing.

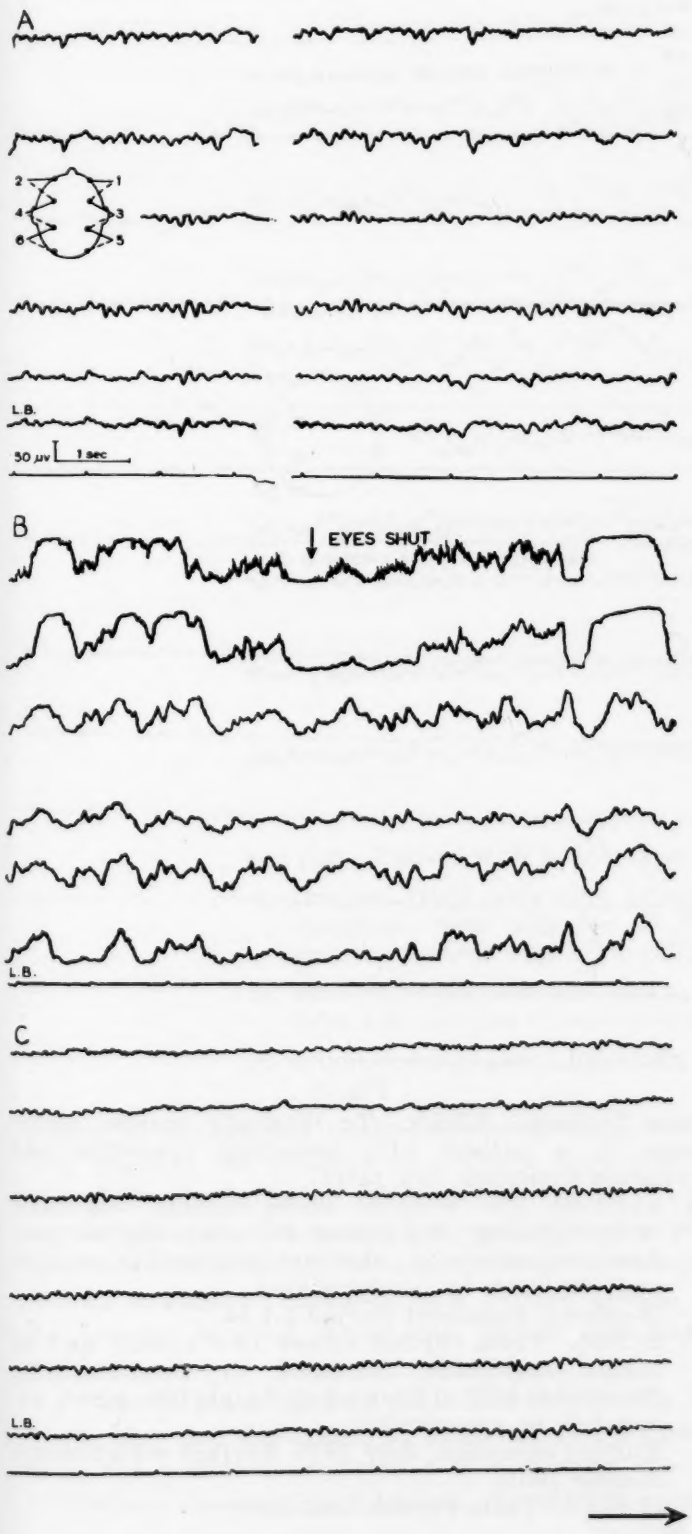
C. 11.2.55. 10 days post-operative. Hormone treatment continued. Further slight improvement.

D. 27.7.55. 8 c/sec. alpha rhythm now present. There were still some 4 c/sec. groups in the occipital areas and some runs of 7 c/sec. waves anteriorly. Throughout these records sharp elements were noticeable.

E. 26.10.55. Alpha rhythm more stable. 4 c/sec. activity further reduced. Overbreathing induced focal right frontal sharp waves.

in amplitude and had increased in rate to 6 c/sec. On 22.6.55. the patient had a greatly improved sense of well-being and was mentally and physically brisker. On repeating his EEG (fig. 5c) the theta rhythm was further reduced and the dominant frequency was now at 8 c/sec.

On other occasion it has been possible to obtain serial electroencephalographic records which have demonstrated the combined effects of hormonal treatment and of operation.



Case 5. Male, aged 32 (R.I. 201495/55) who had suffered from a transient visual disturbance 9 years earlier. Ten months before admission he again began to have visual symptoms and the presence of a chromophobe pituitary adenoma was recognized by the characters of the field defect combined with a enlarged pituitary fossa. He received radiation treatment directed to the pituitary tumour, but one month before admission his vision again became blurred and in addition he appeared profoundly ''hypopituitary''. He was extremely pale and lethargic, preferring to spend the day resting in bed with his eyes shut. His blood pressure was only 96/60 mm. Hg. and his ''water-loading'' test without and with cortisone showed changes typical of suprarenal insufficiency (respectively 8 per cent and 80 per cent of the ''water load'' excreted). The 17-ketosteroid excretion in 24 hours was 1.2 mg., and his B.M.R. was — 33 per cent. The first record was obtained on 24.1.55 (fig. 6a), and it consisted of bursts of 4-5 c/sec. waves and of delta waves. On 26.1.55 he commenced cortisone, 12.5 mg. b.d., thyroid g. 1 daily, and methyl testosterone sublingually, 25 mg. b.d. The next record was made 3 days later and it showed reduced delta activity and increased rate of the theta waves. Accompanying the hormone replacement therapy he rapidly became less apathetic, a pink coloration began to return to his skin and after 5 days of treatment his blood pressure had risen to 110/70 mm.Hg. By 1.2.55. it was considered safe to operate, and by means of a right subfrontal approach a fairly large cystic pituitary chromophobe adenoma was encountered. Eighteen ml. of fluid were withdrawn and an intracapsular removal of the tumour was performed. The pressure on the optic nerves was relieved. The next record was taken 10 days after his operation (fig. 6c) and although there was further reduction in the fast activity (which may have been an early postoperative effect) there was overall no essential change. Five months later (fig. 6d) an 8 c/sec.

Fig. 7

Case 6. Serial EEG's.

A. 14.1.53. Before all treatment. Basic rhythm at 6-7 c/sec. with some 4 c/sec. bursts. Low voltage delta waves were present; maximal in the temporal areas. Overbreathing caused further slowing of the record. Radiation treatment (4,000 r.) given during February, 1953.

B. 18.6.53. Patient clinically worse. Ample bilaterally synchronous delta waves predominate. There is lower voltage 6 c/sec. activity. No change on eye-opening or closure.
Overbreathing impossible.
Exploratory operation performed without removal of tumour 22.6.53.

C. 9.11.55. After hormonal treatment for over 2 years. Main frequency was 6-8 c/sec

alpha rhythm had appeared. At the end of 10 months the record was still further improved (fig. 6e).

It is known that operation on, or radiation treatment of, a pituitary chromophobe adenoma may accentuate features of hypopituitarism by the removal or destruction of functioning remnants of the normal gland. It has been possible to find examples in which there were good clinical grounds for believing that treatment further decreased the function of the anterior pituitary tissue and that this decreased function was responsible for a deterioration in the EEG.

Case 6. A female aged 49 (R.I. 147353/51) who had suffered from a 12-month period of bursting headaches at the age of 42, and whose menopause had occurred at the age of 47, had been aware for 7 months of steadily progressive visual failure. At the time of her first admission she was found to be somewhat hypertensive (blood pressure 180/95 mm. of mercury) and other features of her cardiovascular system made it likely that she would prove a poor operative risk. Accordingly operation was withheld and, during February of 1953, a dose of 4,000r was given to the region of the tumour. An EEG obtained before radiation treatment (fig. 7a) showed a basic rhythm at 6-7 c/sec. The patient returned home after the radiation treatment was completed, but her progress was not satisfactory and coincident with further visual deterioration there was a considerable increase in apathy, sensitivity to cold and the development of skin pallor. By the time of readmission she had become drowsy and disorientated and an EEG obtained on 18.6.53 (fig. 7b) was dominated by ample bilaterally synchronous delta waves in all areas. At an operation, 22.6.53, an extensive chromophobe pituitary adenoma was found, but, in view of the size of the tumour and the patient's general condition no surgical manoeuvre other than verification of the nature of the lesion was attempted. It was decided post-operatively to treat this patient with cortisone, 12½ mg. daily, thyroid, gr. 1 daily, and methyl testosterone 10 mg/day. On this regime her mental state and her sense of well-being improved dramatically, and although her vision remained poor, she was able to increase her physical activity and to run her household with some assistance. A third record was obtained on 12.5.54 and showed a surprising contrast, for without any surgical removal of tumour tissue the tracing had improved considerably. (However, it must be remembered that radiation treatment may produce late effects and the possibility cannot be excluded that some reduction in the size of the tumour occurred between the dates of the second and of the subsequent records.) The delta

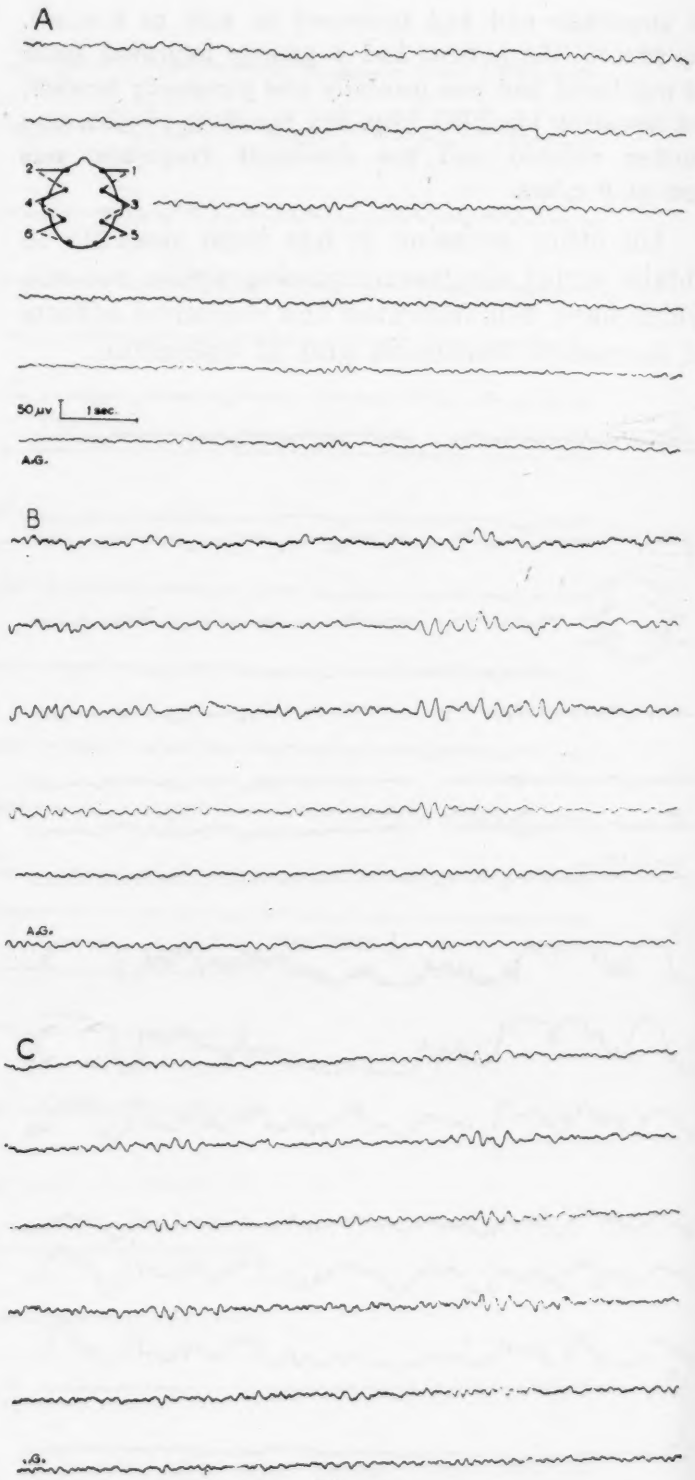


Fig. 8

Case 7. Serial EEG's. To illustrate tumour recurrence in a patient with preceding operative and radiation treatment (see text).

A. 31.12.53. The occipital alpha rhythm responded to eye-opening. Note clear 6-7 c/sec. rhythm predominant anteriorly; this was increased in amount and amplitude by overbreathing.
Hormonal treatment started 7.1.54.

B. 20.7.55. Theta rhythm slower (4-5 c/sec.) and of higher amplitude, increased by overbreathing. There was still a trace of alpha rhythm which responded to eye-opening.
Further operation, July 1955. Further radiotherapy August 1955.

C. 23.11.55. Theta rhythm lessened.

waves had virtually disappeared and were now only present at low voltage, and the main rhythm was once more in the theta range. With the passage of time there was definite further clinical improvement, and by 9.11.55 (which was well over two years after the beginning of the hormonal treatment and was 32 months after the completion of the radiotherapy) the record showed a faster main frequency of about 6-8 c/sec. (fig. 7c). The record was more stable on overbreathing than at her first attendance and, taken as a whole, was now the most ''normal'' of any so far obtained from this patient. This favourable sequence of clinical and electroencephalographic events took place in the presence of a fairly large tumour and under the influence of hormonal agents. These events make an interesting contrast with the next patient where severe endocrine deficiencies and a large tumour co-existed. However, here further growth of the tumour occurred whilst the patient was under observation.

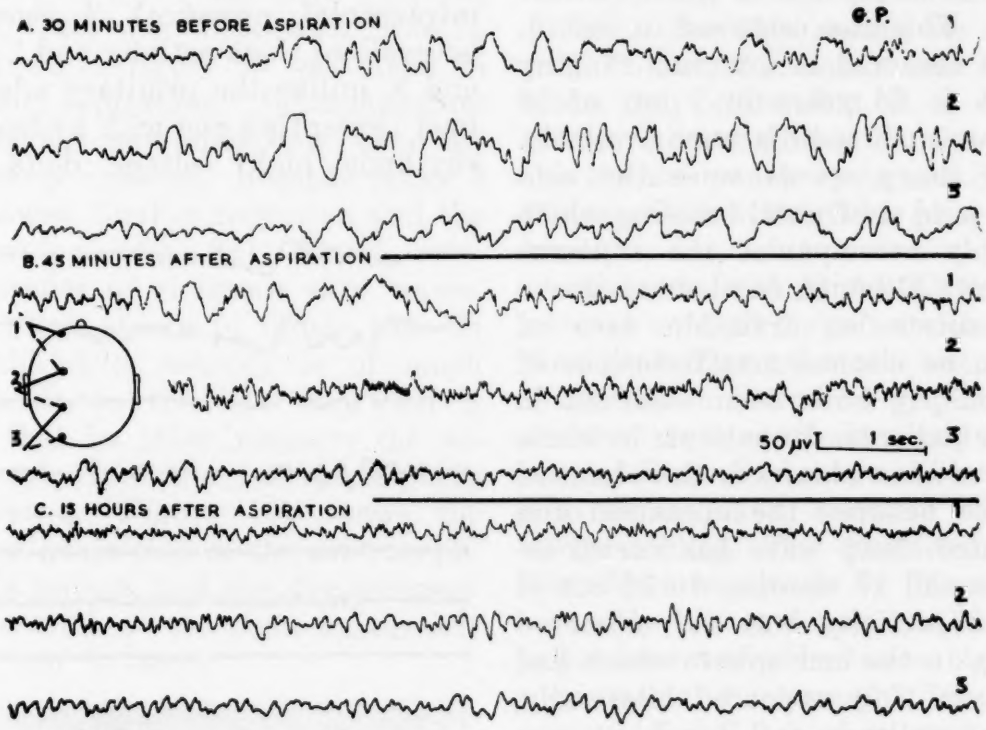


Fig. 9

See text. Patient with Rathké pouch cyst.

A. Drowsy, lying with eyes closed. Could be roused to open his eyes by shouting. Note long run of rhythmic delta waves; in transverse lead recordings these were bilaterally synchronous.

B. Still confused, but now more alert. Note great reduction in rhythmic delta and increase in rate of basic rhythm.

C. Orientated and alert. Rhythmic delta has almost disappeared.

Case 7. Male, aged 40 (R.I. 104648/49) who between May and September of 1949 had had 3 operations for persistent recurrence of symptoms due to a pituitary chromophobe adenoma. At the last operation his right optic nerve was divided and subsequently he had radiation treatment (tumour dose of 5,000 r.). At the time of his first operation the endocrine abnormalities were relatively slight, but by December 1953, when the vision in his left eye was virtually stationary, he showed considerable features of ''hypopituitarism'' with pallor and lack of energy. His EEG (fig. 8a) showed a scanty occipital 8 c/sec. alpha rhythm, whilst a clear 6-7 c/sec. rhythm predominated anteriorly. On 7.1.54 he started on a regime of cortisone, 12½ mg. b.d., thyroid gr. 1 daily, and methyl testosterone, 25 mg. b.d., and clinically he improved considerably. The next record was obtained 18 months later at a time when the symptoms of a recurrence of his tumour, which had been indefinite for about 4 months, had become unequivocal. It showed a more persistent and slower theta rhythm (6 c/sec.). By the time a subsequent record was obtained on 20.7.55 he was somewhat confused and was very apathetic, and it later transpired that he had had amnesia for many of the events of this period. This EEG (fig. 8b) showed pronounced further slowing (4-5 c/sec.) of the theta rhythm and increased amplitude. Following an operation in July

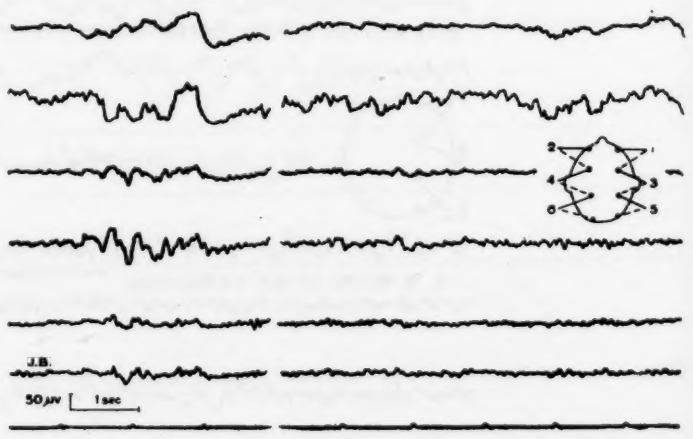
1955, at which time a portion of the tumour sufficient to relieve the pressure on the left optic nerve was removed, he had further radiotherapy, and he made a definite if limited clinical improvement. He became orientated and interested in his surroundings and by November 1955, was able to walk 2-3 miles. A record obtained at this stage revealed some lessening of the theta rhythm and slight return of the faster activity (fig. 8c), but considering the clinical improvement, the record was surprisingly little changed.

In case 5 above the development of frontal focal sharp waves on the side of the operation was mentioned. This also occurred in case 6, and indeed was observed at intervals ranging from 9 months to 16 years in 7 out of 18 patients in whom such records were available. Probably such sharp waves were the consequence of the mild subfrontal bruising which almost inevitably accompanies the exposure of these tumours. Although focal sharp waves presumably indicate an irritable area of cerebral cortex, no clinical manifestations of even minor epilepsy have been observed in these particular patients. In patients in whom serial EEG have been obtained, the observed interval of time between the operation and the first recorded sharp wave has varied between 9 months and 17 months. In 12 out of 18 patients fast activity was also observed post-operatively in the hemisphere which had been exposed; or, if it appeared bilaterally, was of higher amplitude and persistence on the previously exposed side. Another occasional feature of the late post-operative EEG has been the low amplitude of the records but we are uncertain of the significance of this finding.

Rathké pouch cysts

The records of 7 patients over the age of 18 with a Rathké pouch cyst were comparable to those seen among the patients with a pituitary adenoma. That is to say that features ranging from low amplitude to theta dominance were encountered; and from the record alone these 7 patients could not be separated from those with a pituitary adenoma. Of these patients 4 had lesions that mainly or exclusively involved the optic pathways, and there was no significant extension into the third ventricle. In a fifth patient there was some involvement of the third ventricle, and in the remaining cases, although no evidence of raised intracranial pressure was encountered, there was hydrocephalus, and they had the main body of their tumours lying in the third ventricle; in spite of this the records in these 2 patients were not definitely dissimilar from those of patients with a chromophobe pituitary adenoma with little or no compression of this part of the brain.

Among ten other patients with Rathké pouch cysts (of whom 4 had definitely raised intracranial pressure) 2 showed irregular generalized theta activity and "spiky" bursts, and 8, unlike the pituitary adenomata examined (excepting one with hydrocephalus) had rhythmic high voltage delta bursts (1.5-



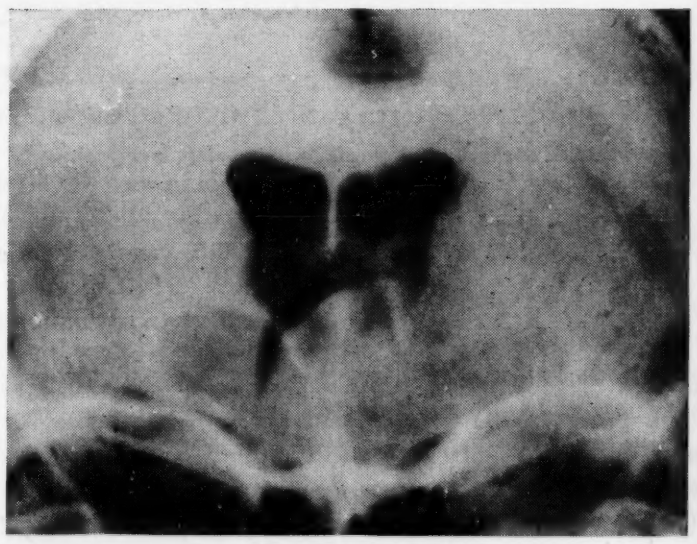


Fig. 10

Above. EEG to show bilaterally synchronous delta bursts predominating on the left.

Below. Pneumoencephalogram. Brow-up antero-posterior projection. Note crescentic deformity of third ventricle produced by left sided basal tumour (Rathké pouch cyst).

2.5 c/sec.). These were usually bilateral, though often with unilateral preponderance and even phase reversal. They were commonly, though not always, inhibited by eye-opening and increased by overbreathing. One such example is shown in figure 9a. Half an hour after this record was obtained the brain was explored through a left frontal burr hole. The frontal horn was tapped and the cerebrospinal fluid was under a pressure of 120 mm. H_2O. The cannula was then advanced into the cyst within the third ventricle and 15 ml. of fluid was withdrawn from it. The record shown in figure 9b was taken 45 min. after this aspiration. In comparison with figure 9a the rhythmic slow wave activity was greatly reduced. Records taken 3 hours later showed further reduction and the following morning (fig. 9c) almost complete disappearance of rhythmic slow waves. Another example is shown in figure 10a. In this patient the delta activity is of much greater amplitude on the left side, and it may be seen that in other respects the recording obtained from the left hemisphere is more disturbed. Figure 10b shows the antero-posterior projection of the air encephalogram of this patient and the displacement of the third ventricle to the right by the left sided tumour can be seen.

DISCUSSION

Among the patients with a Rathké pouch cyst we have endeavoured to make the material most nearly comparable to the group with a pituitary chromophobe adenoma by the exclusion of all cases below the age of 18 years. The assessment of the records of some of these patients was complicated by the occurrence of raised intracranial pressure. However, where the lesion did not compress the third ventricle and was anatomically similar to many of the chromophobe adenomata, it seems likely that metabolic changes were mainly responsible for the abnormalities of the EEG.

It will be recalled that figure 10 illustrated an example of a left-sided tumour which was associated with left-sided predominance of delta bursts; and, in another patient (fig. 9) the cessation of high voltage delta activity followed aspiration of an intraventricular cyst. Although some patients with a large Rathké pouch cyst within the third ventricle did not exhibit rhythmic delta, such activity, when present, is probably associated with direct pressure upon structures in the region of the third ventricle. However, we are aware that such activity may result from hydrocephalus alone, when perhaps dysfunction of the peri-ventricular structures results from distortion of the ventricle with c.s.f.; this subject has been discussed in considerable detail by Daly, Whelan, Bickford and McCarty (1953). For this reason we would disagree with Tönnis, Steinmann and Krenkel (1953) when they state that it is likely that the grosser abnormalities of the EEG's among the Rathké pouch cysts are due to the fact that the lesion has been present from childhood.

Abnormalities of the EEG resulting from adrenal cortical hypofunction are known to disappear after treatment with cortisone. The changes seen include a gradual reduction of the slow wave component and a return to the normal frequency range of the resting record, with an increased stability of the record to overbreathing. The first clear statement to this effect was made by Thorn (1949). Subsequently it was demonstrated that electrical improvement was dependent specifically upon cortisone and although deoxycorticosterone acetate (D.O.C.A.) might produce clinical and biochemical improvement it did not significantly affect the EEG (Cloche, Azerad and Stuhl 1952). In our experience the improvement in the EEG which results from cortisone treatment does not of necessity match detectable changes in alertness and in the mental state of the patient. For example, in figures 3b and 3c the EEG was not as "normal" as would have been expected from the state of the patient. Again, figure 6c is less abnormal than is figure 6b and certainly there was no change in the alertness of the patient at the times of these two records. The possibility of a discrepancy existing between the mental state and the degree of electrical abnormality in Addison's disease has already been mentioned by Romano and Engel (1944).

Since cortisone became available it has become evident that some degree of suprarenal failure in association with chromophobe ade-

nomata is far commoner than was hitherto supposed. As far as we are aware it is only deficiency of the adrenal cortex (Engel and Margolin 1942; also Hoffman, Lewis and Thorn 1942) and of the thyroid gland (Bertrand, Delay and Guillain 1938), which significantly influence the EEG. Of these two it is clear that adrenal cortical hypofunction produces the more profound effects and, for instance, Piaggio Blanco, Austt, Achard, Canabal and Dighiero (1950) indicated that myxoedema secondary to anterior pituitary failure could be distinguished electroencephalographically from primary myxoedema. A study of their paper and its illustrations leaves little doubt in our minds that this differentiation is possible because of features resulting from an associated secondary adrenal cortical deficiency. This possibility was considered by these authors, but they drew no firm conclusion. Primary myxoedema, according to Austt (1950), results in slowing of frequencies and considerable reduction in voltage. In addition, in very long standing cases the alpha rhythm is said to disappear and a few high voltage slow waves may be seen (Bertrand, Delay and Guillain 1938). The changes in the EEG which occur with suprarenal insufficiency have recently been well described by Cloche, Azerad and Stuhl (1952). These authors in a detailed study of 9 patients observed that the most frequent abnormal rhythm was in the theta band (5-7 c/sec.) and that this rhythm was of moderately high voltage and predominated in the anterior leads. The alpha rhythm was "slowed", and there was also loss of faster activities which was partly responsible for a uniform appearance of the records. High voltage delta waves were noted in the resting record in 5 cases. Overbreathing did not influence the record of 4 patients, but in 3 it increased the slow waves and in another patient it brought out large slow 3 c/sec. waves. Hoffman, Lewis and Thorn (1942) had previously suggested that great sensitivity of the record to overbreathing was one of the features of adrenal cortical failure. The discrepancy between these two groups of workers in the effects of overbreathing may have been due to differing levels of blood sugar in the two groups of patients (cf. Engel and Margolin 1942). It may well be that the level of blood sugar at which sensitivity of the record to overbreathing in adrenal cortical hypofunction is manifested drops considerably after the administration of cortisone. This can be suggested following an isolated report by Bricaire, Misès, Dreyfus-Brisac and Fischgold (1953) that in an Addisonian patient instability of the record upon overbreathing was present with a blood sugar level of 80 mg/100 ml., and was absent when the blood sugar was 160 mg/100 ml.; following treatment with cortisone the record remained stable when overbreathing was performed in the presence of a blood sugar of 90 mg/100 ml. In our material there is insufficient information to allow us to comment further on these possibilities except to record that increased stability of the record on overbreathing invariably accompanied treatment with cortisone.

It will be observed that the electroencephalographic changes described in primary adrenal cortical hypofunction (Cloche, Azerad and Stuhl 1952) do not differ from those found in the majority of patients with a pituitary chromophobe adenoma except for the presence of asymmetry between the hemispheres. Tönnis, Steinmann and Krenkel (1953) ascribed the bilateral theta rhythm among patients with a pituitary chromophobe adenoma primarily to alteration of water metabolism, with a tendency to water retention. It is known that the metabolism of water is abnormal in suprarenal deficiency (Levy, Power and Kepler 1946), and can be rectified by the administration of cortisone (Oleesky and Stanbury 1951). To try to decide whether disturbed water metabolism affects the EEG more profoundly than the other metabolic consequences of suprarenal deficiency seems to us unprofitable at the moment. It is sufficient to be aware that adrenal cortical hypofunction is the factor which most profoundly influences the EEG in the majority of patients with a pituitary chromophobe adenoma. This last statement has recently gained indirect support from Hughes and Summers (1956). They reported changes in the EEG in the hypopituitary state consequent upon

post-partum necrosis of the pituitary. The alpha rhythm was greatly reduced and the feature of the records was a generalized theta activity at 4.0-6.5 c/sec.

Tönnis, Steinmann and Krenkel (1953) remarked that in all cases of pituitary tumour in which the record showed asymmetry of frequencies between the two hemispheres, there was evidence of an extrasellar lesion. Our results support this finding, and we should like to suggest that pressure from a basal mass exerted asymmetrically causes the manifestations of a metabolic disorder to be unequally apparent in the two hemispheres. But the fact that the record may remain symmetrical (e.g. fig. 5) or even all-but normal (e.g. fig. 1) in the presence of suprasellar extension of a pituitary adenoma must not be overlooked.

From the findings in this survey we wish to state that the study of patients with pituitary chromophobe adenomata should not be regarded as complete until an EEG has been obtained. Further experience may prove that this examination can sometimes be the most sensitive indicator of secondary suprarenal hypofunction. The EEG would perhaps be rendered even more informative if it included the effects of overbreathing obtained when the patient's blood sugar was no higher than 80 mg. per 100/ml. It is possible, also, that increased information could be obtained by the use of a nasopharyngeal lead (cf. Fauré, Jasper and Henderson 1948). Finally, when present, the finding of focal abnormalities in the records of these patients may give the lead in the detection of otherwise unsuspected massive suprasellar extensions of these tumours.

SUMMARY

1. One hundred and two electroencephalograms from 59 patients with a pituitary chromophobe adenoma and 32 EEG's from 17 patients with a Rathké pouch cyst have been reviewed.

2. The records of those with a pituitary chromophobe adenoma could be divided as follows: the bulk of the records showed a clear theta rhythm (4-7 c/sec.) which was often asymmetrical. Of the remainder, 10 were normal or borderline normal; 9 were of low voltage; and 3 showed generalized delta waves.

3. Although similar features occurred among some of the patients with a Rathké pouch cyst, recordings in the presence of a Rathké pouch cyst frequently showed bilaterally synchronous rhythmic delta bursts (1.5-2.5 c/sec.) such as were only once observed with a pituitary chromophobe adenoma.

4. Serial EEG's have been obtained in many of these patients, and it has usually been possible to demonstrate recession of the abnormal activity with hormone replacement therapy (cortisone, thyroid and sometimes testosterone). It is known that symmetrical theta activity may occur as a manifestation of suprarenal failure and that it can be dispersed by treatment with cortisone.

5. It is our belief that many of the EEG abnormalities commonly ascribed to pituitary tumour are in fact caused by associated endocrine deficiencies. However, it seems possible that the asymmetries of the record in these patients are associated with asymmetrical pressure upon structures at the base of the brain.

6. The possible value of the EEG in the diagnosis and management of these patients is discussed.

We are indebted to Mr. Joe Pennybacker for permission to record clinical details of the patients admitted to the Department of Neurosurgery. We are also grateful to Mr. Pennybacker and to Dr. C. W. M. Whitty for helpful criticism and advice.

Several of the records were made by Miss F. M. Taylor and her assistance is gratefully acknowledged.

During the preparation of this paper one of us (A.A.J.) held a Nuffield Foundation Fellowship.

REFERENCES

Austt, E. G. Quoted in Piaggio Blanco, R. A., Austt, E. G., Achard, L. P., Canabal, E. J. y Dighiero, J. **1950**, *loc. cit.*

Baudouin, A., Puech, P., Fischgold, H. et Lerique-Koechlin, A. L'électroencéphalographie dans les tumeurs cérébrales. *Semaine Hôp.*, Paris, **1946**, *26*: 1226-1233.

Bertrand, I., Delay, J. et Guillain, J. L'électroencéphalogramme dans le myxoedème. *C. R. Soc. Biol.*, Paris, **1938**, *129*: 395-398.

Bricaire, H., Misès, R., Dreyfus-Brisac, C. et Fischgold, H. Initiation à l'électroencéphalographie: EEG d'un cas de maladie d'Addison. *Presse méd.*, **1953**, *61*: 750-751.

CLOCHE, R., AZERAD, E. et STUHL. Les modifications de l'électroencéphalogramme dans l'insuffisance surrénale. **1952**, *Ann. Méd.*, *53*: 689-708.

COBB, W. A. Ch. ix. in *Electroencephalography*, London, edited by Denis Hill and Geoffrey Parr, Macdonald & Co., **1950**.

DALY, D., WHELAN, J. L., BICKFORD, R. G. and MACCARTY, C. S. The electroencephalogram in cases of tumours of the posterior fossa and third ventricle. *EEG Clin. Neurophysiol.*, **1953**, *5*: 203-216.

ENGEL, G. L. and MARGOLIN, S. G. Neuropsychiatric disturbances in internal disease, metabolic factors and electroencephalographic correlations. *A. M. A. Arch. Int. med.*, **1942**, *70*: 236-259.

FAURÉ, J., JASPER, H. H. et HENDERSON, L. Etude électroencéphalographique des lésions de la base du cerveau par la dérivation basale. *Rev. Neurol.*, **1948**, *80*: 596-605.

HOFFMAN, W. C., LEWIS, R. A. and THORN, G. W. The electroencephalogram in Addison's disease. *Bull. Johns Hopk. Hosp.*, **1942**, *70*: 335-361.

HUGHES, R. R. and SUMMERS, V. K. Changes in the electroencephalogram associated with hypopituitarism due to post partum necrosis. *EEG Clin. neurophysiol.*, **1956**, *8*: 87-96.

LENNOX, M. A. and BRODY, B. S. Paroxysmal slow waves in the electroencephalograms of patients with epilepsy and sub-cortical lesions. *J. nerv. ment. Dis.*, **1946**, *104*: 237-248.

LEVY, M. S., POWER, M. H. and KEPLER, E. J. Specificity of "water test" as diagnostic procedure in Addison's disease. *J. Clin. Endocrinol.*, **1946**, *6*: 607-632.

OLEESKY, S. and STANBURY, S. W. Effect of oral cortisone on water diuresis in Addison's disease and hypopituitarism. *Lancet*, **1951**, ii: 664-666.

PIAGGIO BLANCO, R. A., AUSTT, E. G., ACHARD, L. P., CANABAL, E. J. y DIGHIERO, J. Alteraciones electroencefalográficas y electrocardiográficas en dos casos de mixedema secundario (Mixedema pituitario). *Arch. urug. med.*, **1950**, *37*: 167-182.

ROMANO, J. and ENGEL, G. L. Delirium, 1. EEG Data. *Arch. Neurol. Psychiatr.* Chicago, **1944**, *51*: 356-377.

THORN, G. W. Clinical and metabolic changes in Addison's disease following the administration of compound E. acetate (11-Dehydro-17-hydroxycorticosterone acetate). *Tr. A. Amer. Physicians*, **1949**, *62*: 233-244.

TÖNNIS, W., STEINMANN, H. W. und KRENKEL, W. Electroencephalographische befunde bei 44 Tumoren der sellagegend. *Acta Neuroveg.*, **1953**, *5*: 291-305.

Reference: BOSELLI, F. and JEFFERSON, A. A. Electroencephalogram with chromophobe adenomata and Rathké pouch cysts: modification by associated metabolic disorder. *EEG Clin. Neurophysiol.*, **1957**, *9*: 275-290.

PRINTED IN CANADA

ELECTROGRAPHIC STUDY OF THALAMIC IMPULSES TO THE STRIATUM AND PALLIDUM [1]

E. A. SPIEGEL, M.D., E. G. SZEKELY, V. M.D. and W. W. BAKER, Ph.D.

Department of Experimental Neurology, Temple University School of Medicine, Philadelphia, Penna.

(Received for publication: August 2, 1956)

The starting point of this study was the well known observation that involuntary movements caused by diseases of the so-called extrapyramidal system are increased by sensory and emotional stimuli, while they decrease in sleep. In view of the role which the diencephalon plays in the mechanism of emotions and in the alternation between the waking and the sleeping state, it was hoped that a study of thalamic impulses to the striopallidum may shed some light on these phenomena.

ANATOMICAL DATA

In comparative-anatomic studies on mammals frequently fine fibers can be found in the caudate nucleus that can be followed into the internal capsule (Spiegel 1919). There is, however, little agreement among anatomists regarding the projection of various thalamic nuclei upon the striatum and pallidum. For the centrum medianum, one group of authors (Walker 1938; Mettler 1945; Glees and Wall 1946) assumed a connection with the pallidum, that is, however, not accepted by the Vogts (1941) and by McLardy (1948) who arrived at the conclusion that the impulses from this nucleus reach the striatum. Similarly Hassler (1949) describes a projection to the fundus striati, and Droogleever-Fortuyn and Stevens (1951) assume that only the putamen and claustrum receive impulses from this nucleus.

The intralaminar and midline nuclei send impulses to the caudate nucleus according to Droogleever-Fortuyn and Stevens; similarly Cowan and Powell (1955) find that the intralaminar nuclei project to the head of the caudate, the parafascicular nucleus to the putamen, while Hassler (1949) describes connections from the lamina medullaris to the pallidum and from the nucleus parafascicularis to the most medial part of the striatum (Fundus striati of Brockhaus).

There is also no agreement regarding the projection of the nucleus ventralis anterior. It sends impulses to the striatum according to Walker, to the pallidum according to Ranson (1942). Kuhlenbeck (1954) thinks that this nucleus may have reciprocal relationships to the pallidum, putamen and caudatus.

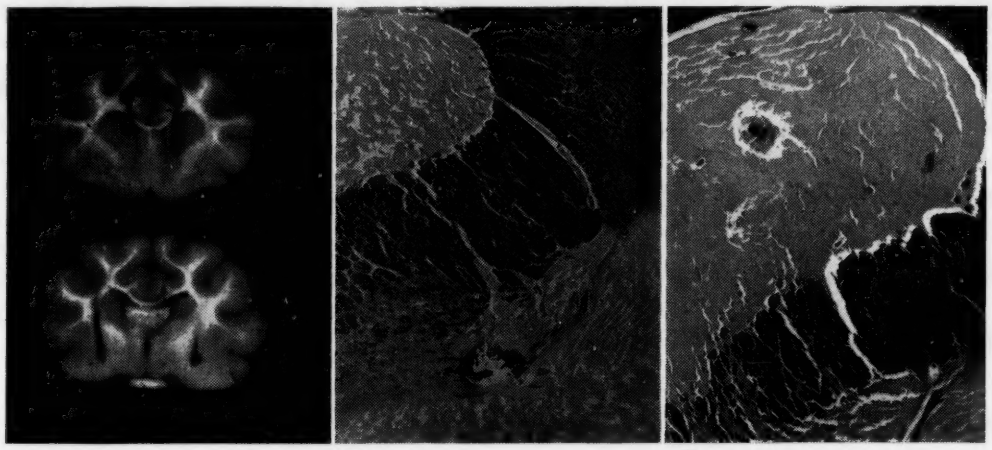
For the dorsomedial nucleus Papez assumes a connection to the pallidum while Glees and Wall (1946) draw connections to the nucleus centrum medianum from which a projection to the pallidum may exist. In the older literature there is a statement by Sachs (1909) that the anterior nucleus projects to the striatum. More recent authors do not mention such a connection. In contrast to the above mentioned authors who described some degenerative changes in thalamic nuclei after striatal lesions, Nashold, Hanbery and Olszewski (1955) failed to find changes in the thalamus following small lesions of the caudate nucleus or putamen in cats and monkeys. They conclude that the thalamic projections to the striopallidum are either not extensive or formed by collaterals.

In view of these difficulties of anatomic investigations, a systematic electrographic study seemed of interest. In this respect, there are only occasional observations from Magoun's laboratory. Surprisingly these authors were only able to record changes in the electrical activity of the caudate nucleus but not in the pallidum.

[1] Aided by Grant No. B-470 of the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Dept. of Health, Education and Welfare.

METHOD

Experiments were carried out on 130 cats. In one group a 3 per cent solution of strychnine sulfate, 0.01 - 0.02 cc., or penicillin in oil, 0.02 cc., was injected in curarized animals in various parts of the thalamus. In the second group, electric pulses obtained from a Grass Stimulator (pulse duration 2 msec; 4-20V., only occasionally 30 V.; electrode resistance 30-70,000Ω) were applied by means of concentric needle electrodes in cats under Dial anesthesia. The electric discharges of the basal ganglia were lead off by depth electrodes (average resistance 30,000Ω) and those of the cerebral cortex by epidural electrodes; usually bipolar, occasionally also monopolar tracings were obtained on an inkwriting electroencephalograph and a cathode ray oscilloscope. Stimulating as well as recording electrodes were inserted stereotactically. Their position was always checked anatomically and in important cases in histologic serial sections stained by the Weil method (fig. 1).



A B C

Fig. 1

A. Cat 77. Electrode in the caudate nuclei and pallida (corresponding records in fig. 3 A-C).
B. and C. Cat 109. B. Electrode in the globus pallidus, C, electrode in the caudate nucleus (corresponding record in fig. 3 G).

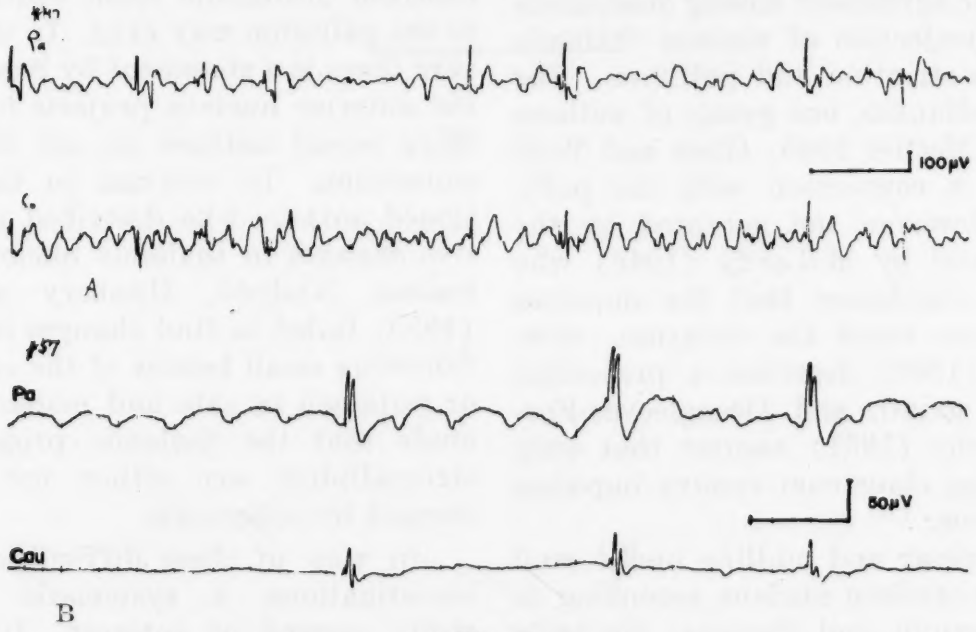


Fig. 2

Effect of local strychninization.
A. Cat 47, curarized, 5 min. after injection of 3 per cent strychnine sulf. 0.01 cc. into the dorsomedial nucleus. Monopolar records from the pallidum (Pa) and frontal cortex (Co).
B. Cat 57, curarized, 5 min. after injection of 3 per cent strychnine sulf. 0.02 cc. into the dorsomedial nucleus. Bipolar records from the pallidum (Pa) and caudate nucleus (Cau).

RESULTS

Strychnine injections. Injections into the dorsomedial nucleus, into the nucleus ventralis anterior or into the centrum medianum produce single or multiple spikes that may appear in more or less rhythmic intervals (fig. 2). On injection into the dorsomedial nucleus, such reactions were obtained in the caudate nucleus as well as in the globus pallidus, while on injection into the nucleus ventralis anterior (VA) or into the centrum medianum (CM) pallidal reactions prevailed. However, on injection into rather small nuclei one has to bear in mind that the fluid easily diffuses to adjacent cell groups, even if it is limited to 0.01 - 0.02 cc. Anatomic examination following injection into the dorsomedial nucleus, for instance, revealed not infrequently that the solution that had been stained with methylene blue had reached the periventricular gray and/or the region of the intralaminar (IL) nuclei, so that stimulation of these cell groups could not be excluded. We felt, therefore, that definite localizing conclusions from strychnine injections are hardly permissible if one deals with these relatively small nuclei. Consequently most of our experiments were devoted to electric stimulation.

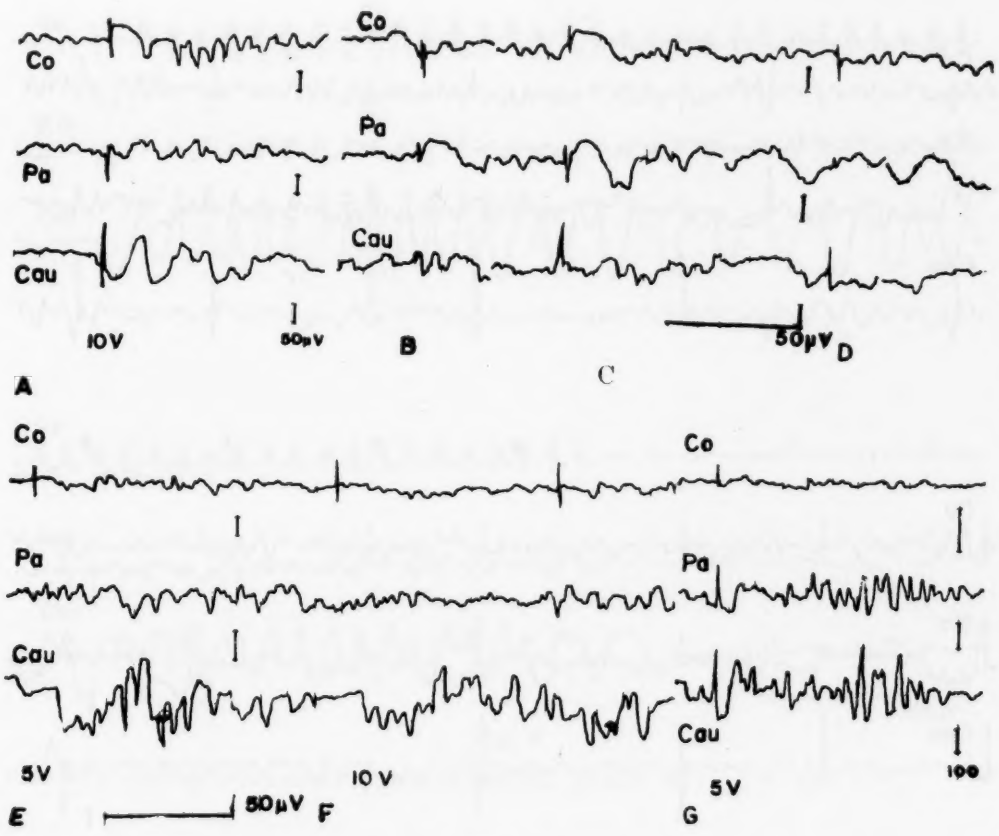


Fig. 3

Effect of single electric pulses.

A. Cat 77. Stimulation of the nucleus ventralis ant.; slow waves in caudate nucleus (Cau) and frontal cortex (Co), no reaction in the pallidum (Pa).

B. C. D. Cat 77. Stimulation of the dorsomedial nucleus. Reaction in the pallidum and cortex only (B, 10 V., C, 20 V.). D. Repetition of stimulation after electrolytic lesion of the area of stimulation (no effect with 30 V.).

E. F. Cat 84. Stimulation of the anterior part of the nucleus ventralis lateralis. Spindle formation in the caudate nucleus only. Note long latent period (about 0.2 sec.) before beginning of spindle formation and ineffectiveness of stimulus during spindle. Stimulating electrode: resistance 55,000 Ω.

G. Cat 109. Stimulation of nucl. ventralis anterior. Spindle formation in pallidum (Pa) and caudate nucleus (Cau).

Electric stimulation. Single electric impulses elicit single or multiple waves, the duration of which may vary between 0.04 and 0.3 sec. (fig. 3 and 4). On repeated stimula-

tion at regular intervals, for instance every 2 sec., not only the duration but also the height of these waves may show periodic fluctuations. The waves may appear rather independently in the caudate nucleus and in the pallidum, for instance figure 3 A shows them in the caudate nucleus only, figure 3 B and 3 C in the pallidum only. After electrolytic destruction of the area of stimulation in the dorsomedial nucleus (fig. 3 D), a reaction in the pallidum no longer appeared, although a higher voltage was used in 3 D after the electrolysis than in the preceding stimulations.

A further type of reaction observed, particularly on stimulation of the nucleus ventralis anterior and of the intralaminar nuclei, is the appearance of groups of waves with a frequency of 6-7/sec. similar to spontaneous spindles, either in the caudate nucleus alone (fig. 3 E, F) or in both ganglia (fig. 3 G). Stimulation during a spontaneous or induced spindle (fig. 3 F) usually is ineffective. While the latent period of the single waves varies between 10 and 30 msec., the appearance of the first wave of the spindle formation may be delayed up to 200 msec. (fig. 3 E, F). With repeated stimulation, particularly of the nuclei of the non-specific

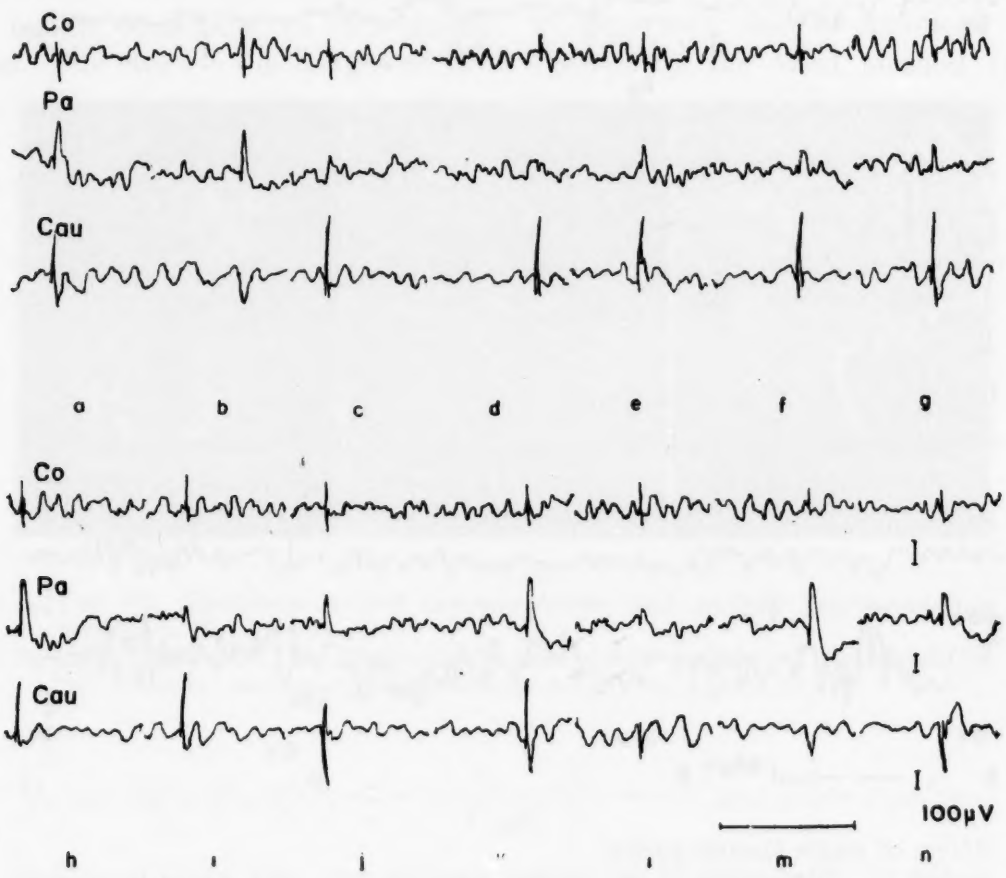


Fig. 4

Cat 92. Fluctuations in the amplitude of the pallidal reaction a to n: Stimulation of the nucl. centrum medianum every 2 sec. Stimulus 30 V., 15 μ A., 2 msec.

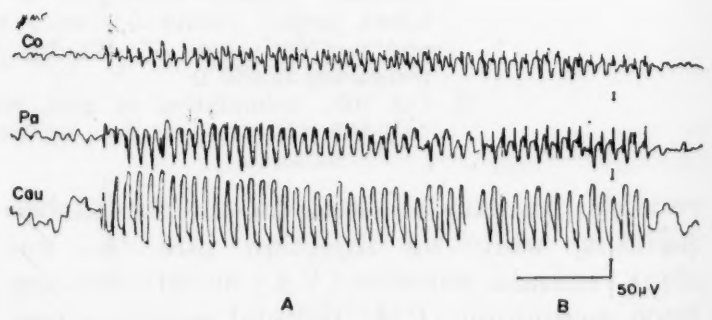


Fig. 5

Cat 105. Recruitment in pallidum (Pa) and caudate nucleus (Cau) on stimulation of the lamina medullaris interna (5 V., 8.5/sec.). Between A and B continuous stimulation for 8 sec.

system at frequencies between 4 and 10/sec., recruitment phenomena were elicited as described by Starzl and Magoun (1951). However, also these reactions are not limited to the caudate nucleus, but may also be recorded from the pallidum (fig. 5). Stimulation of the nucleus ventralis posterior may induce rudimentary recruitment, particularly in the caudate, or high amplitude waves at the rhythm of stimulation or at a lower frequency (fig. 6 and 7). On prolonged stimulation, the high amplitude oscillations may be followed by an alternans type with high and low amplitude waves alternating in the rhythm of stimulation (fig. 6), or groups of waves in that rhythm and with low amplitude may

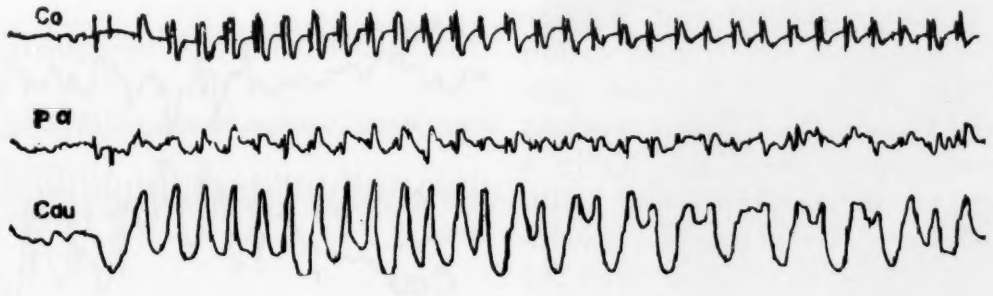


Fig. 6

Cat 113. Stimulation of the nucleus ventral. poster. 4 V.

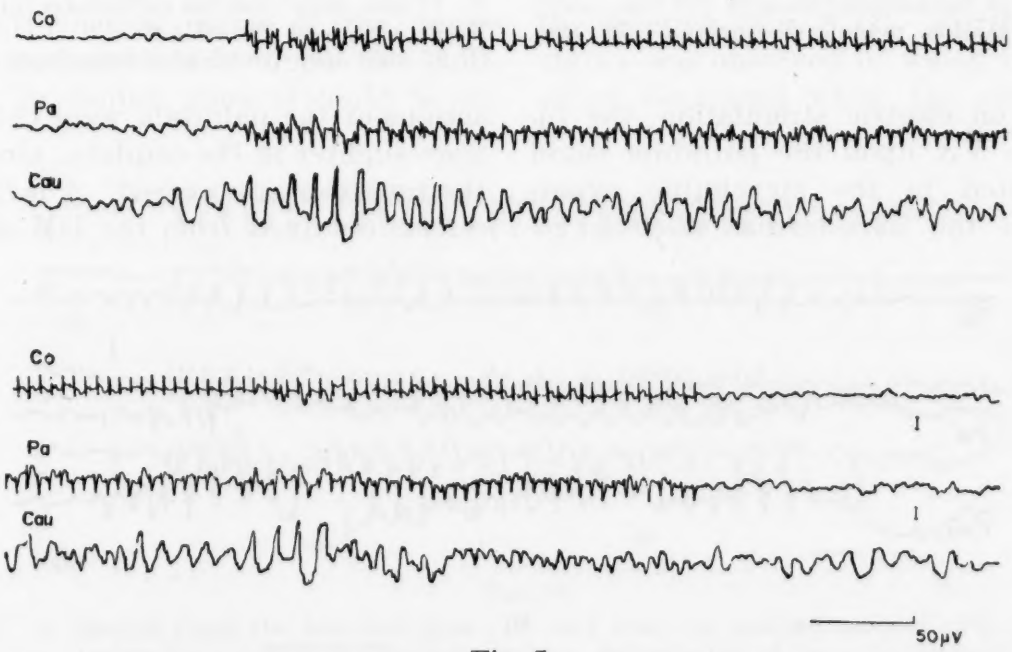


Fig. 7

Cat 113. (Same as in fig. 6). Stimulation of the nucleus ventral poster. 4 V., 8.5 stim/sec.

be combined with groups of oscillations of lower frequency and high amplitude (fig. 7).

Origin of the reaction: Thalamic impulses reaching the striopallidum originate not only in the nuclei of the so-called nonspecific projection system, but also in association nuclei (anterior and dorsomedial nucleus) and to a certain extent in the nucleus ventralis posterior. However, the influence of the nonspecific nuclei is more constant and definite than that of the association nuclei and, within the former nuclei, the effect is most pronounced from the IL and the VA, the weakest and least constant from the CM. While a definite effect upon the caudatus and pallidum could be observed from the IL, the influence of the VA was more marked upon the caudate than upon the pallidum. More frequently than on electric stimulation, the influence of the VA upon the pallidum could be demonstrated in the strychnine experiments. From the dorsomedial nucleus reactions of the pallidum were obtainable; they were slighter in the caudate. Only in one case the reverse was observed. A large part of the effects obtained from the DM may be due to

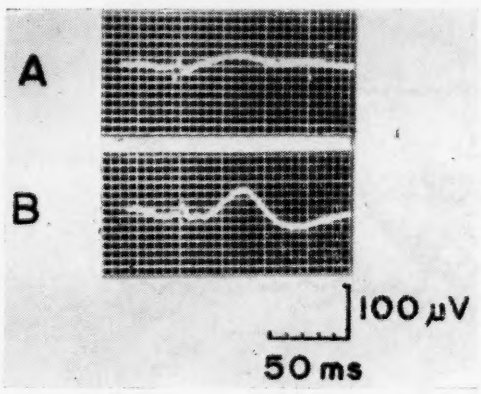


Fig. 8

Cat 85. Pallidal reaction on stimulation (20 V.) of A: the ventral part of dorsomedial nucleus (18 mm. deep) and B, of the lamina medullaris interna (19 mm. deep).

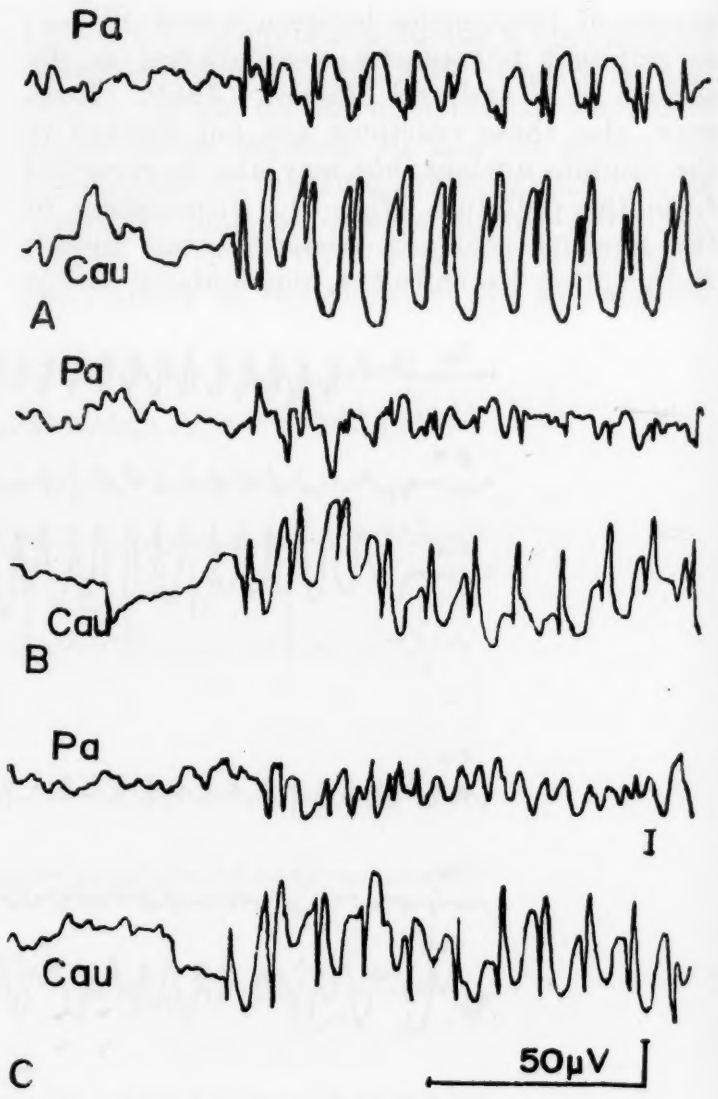


Fig. 9

Cat 105. Stimulation at various levels, 5 V., 5/sec.
A. 21 mm. deep (lamina medullaris interna).
B. 23 mm. deep (Forel's field).
C. 25 mm. deep (outside of mamillary body).

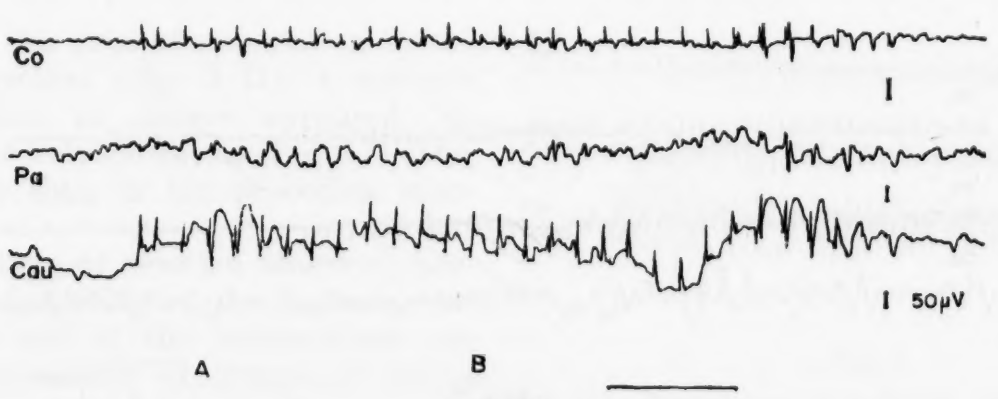


Fig. 10

Cat 108. Hypothalamic stimulation. Rudimentary reaction in the caudate nucleus, 5 V., 5/sec. Between A and B continuous stimulation for 10 sec.

spread to IL. Such an interpretation is supported by experiments in which the electrode was lowered millimeter by millimeter from the area of the dorsomedial nucleus into that of the lamina medullaris interna. Sometimes it could be noted that stimulation of the most ventral part of the dorsomedial nucleus was ineffective, but further lowering of the elec-

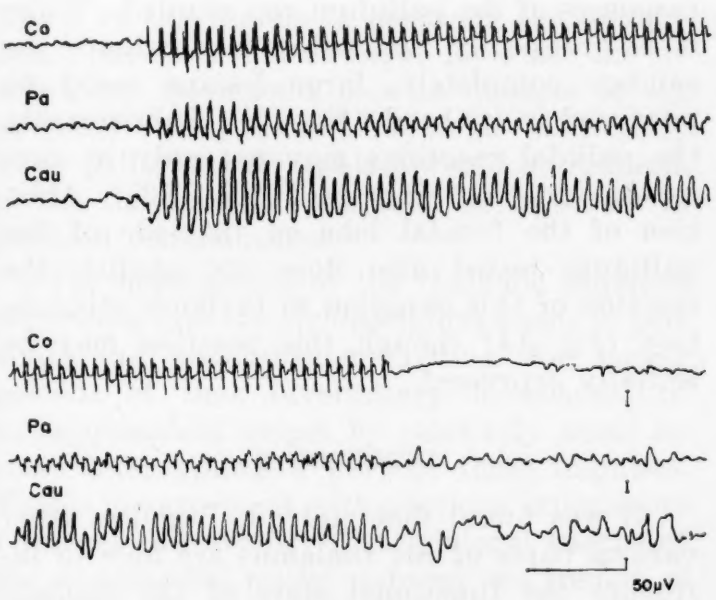


Fig. 11
Cat 110. Stimulation of the lamina medullaris externa.

Fig. 12
Cat 123. Lesion of the left caudate nucleus.

trode tip by one millimeter into the region of the lamina medullaris interna produced definite reactions (fig. 8). However, an independent influence of parts of the dorsomedial nucleus, particularly upon the pallidum can not be denied, since it could be demonstrated in stimulation with single pulses that electrolysis of the area of stimulation in the dorsomedial nucleus was able to abolish the reaction (fig. 3 D). Furthermore an instance was observed in which the stimulating effect decreased when the electrode in the

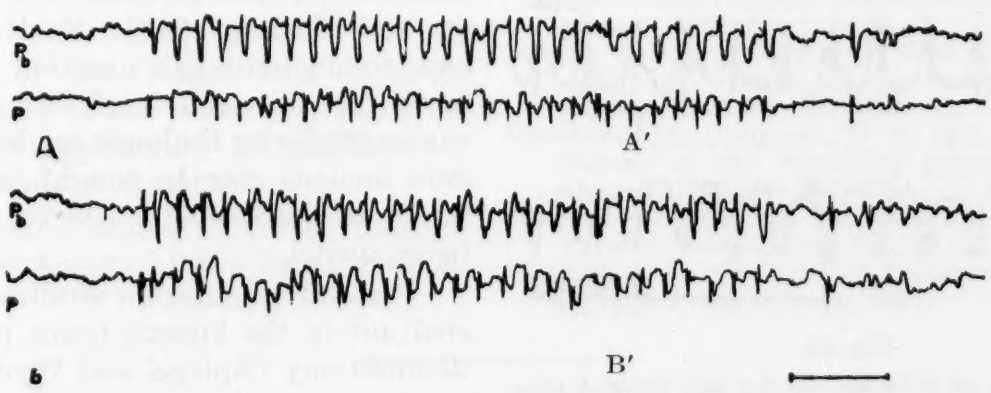


Fig. 13

A. Record from the left pallidum (P) and from its ventral surface (Pb) before the lesion in the caudate nucleus. Stimulation of the anterior part of the left nucleus ventralis lateralis, at 10 V.

B. Repetition of the stimulation with the same parameters after the lesion. Between A and A′ and B and B′ respectively continuous stimulation for 6 sec.

dorsomedial nucleus approached the IL. From the AN a weak reaction in the caudate nucleus could be observed in some instances; on insertion of the electrodes into the adjacent VA, the reaction definitely increased as a rule. When the electrode was lowered beyond the lamina medullaris interna into the subthalamus the recruitment reaction decreased definitely (fig. 9). On hypothalamic stimulation, at the most occasional rudimentary reactions were noted (fig. 10). Whether the recruitment obtained on stimulation of the region of the lamina medullaris externa (fig. 11) is due to stimulation of cell groups of this area or of fibers passing through it could not be decided.

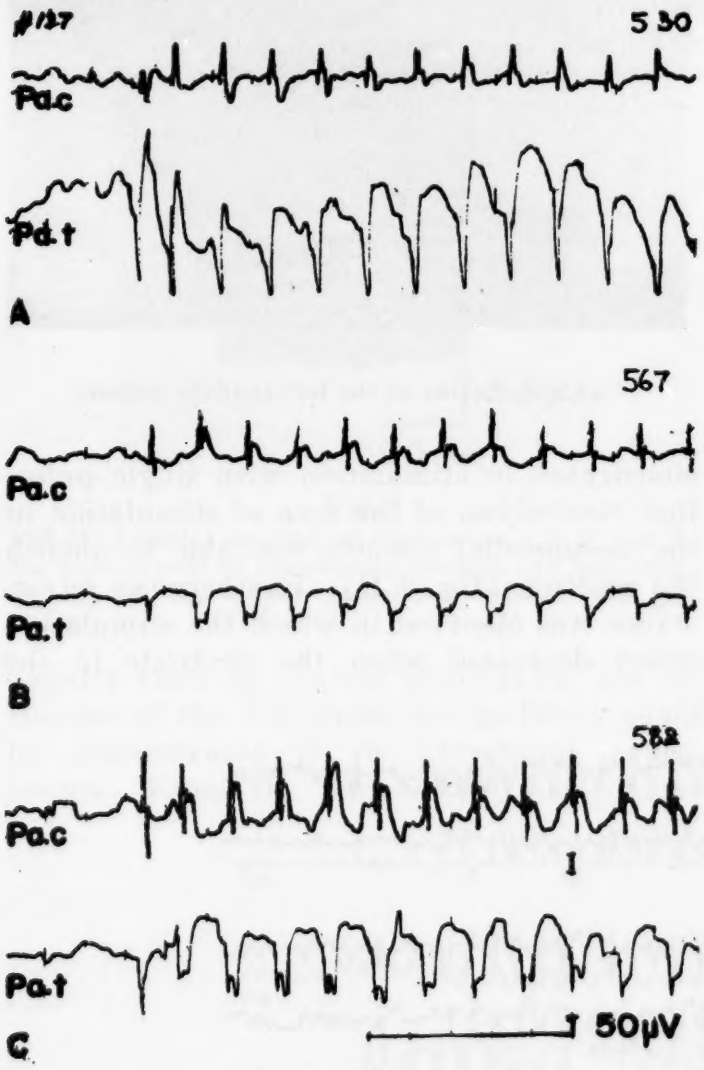


Fig. 14

Cat 127. Effect of ablation of the left frontal lobe. Stimulation of the left n. ventral. anter. at 10 V., 4/sec. Record from the center (Pa.c.) and dorsal part (Pa.t.) of the pallidum.
A. Frontal lobe intact.
B. A few minutes after.
C. 1½ hours after ablation of the left frontal lobe.

Pallidal reaction following striatal lesions and ablation of the frontal lobe. It has been mentioned that pallidal reactions appeared not only simultaneously with striatal responses, but also independently (fig. 3B; 4). This independence of the former reactions from the striatum is further demonstrated by experiments in which the influence of lesions in the caudate nucleus upon the responses of the pallidum was studied. While it is practically impossible to eliminate the caudate completely, large lesions could be produced in its head (fig. 12). Subsequently the pallidal reactions may not only be preserved but even increased (fig. 13). Ablation of the frontal lobe on the side of the pallidum tested also does not abolish the reaction of this ganglion to thalamic stimulation (fig. 14) though this reaction may be initially depressed.

DISCUSSION

It was found that multiple impulses from various parts of the thalamus are able to influence the functional state of the caudate nucleus and of the globus pallidus. This influence is not restricted to the nuclei of the so-called nonspecific projection system but is also demonstrable, at least to a certain extent, from the association nuclei and the relay nuclei of a main sensory system such as the nuclei ventrales posteriores. It is possible that the type of reaction observed on stimulation of these latter nuclei is related to the "augmenting responses" observed in the sensory cortex on their stimulation (Dempsey and Morison 1943). Further studies will have to elucidate this question. The anatomic basis for this effect of stimulation of the ventro-posterior thalamic nuclei upon the caudate nucleus may be sought in striatal collaterals of corticopetal fibers originating in these nuclei.

Parallel stimulation studies are being carried out in the human brain preceding pallido-ansotomy (Spiegel and Wycis 1956). Such studies are, of course, not possible to the same extent as in experimental animals. It could, however, be shown that stimulation of the region of the lamina medullaris interna in the human brain is also able to elicit re-

cruitment phenomena in the pallidum. It may, therefore, be permissible to suggest inferences from the present findings regarding pathologic problems. If it is true that the functional state of the basal ganglia is closely related to that of various parts of the thalamus, as our experiments indicate, then it becomes understandable that sensory or emotional stimuli, by increasing the state of excitation of the thalamus, augment the pallidofugal impulses that cause or facilitate the involuntary movements seen in diseases of the so-called extrapyramidal system. Conversely these pallidofugal impulses would be reduced, if the thalamus is quiescent as in states of reduced consciousness.

The multiplicity of the thalamic impulses streaming into the striopallidum seems to preclude the possibility to reduce for longer periods of time involuntary movements of extrapyramidal origin by relatively small lesions interrupting a part of these impulses. This is in agreement with previous experiences (Spiegel and Wycis) that bilateral lesions of the dorsomedial nuclei reduced the tremor of paralysis agitans only temporarily if at all, so that operations designed to reduce such involuntary movements have to be directed to the efferent parts of the basal ganglia.

SUMMARY

1. Electrographic studies show that multiple thalamic impulses reach the caudate nucleus and/or globus pallidus. These findings indicate a close relationship between the functional state of the thalamus and that of the striopallidum.

2. Ablation of the frontal lobe or large lesions in the head of the caudate nucleus do not prevent the appearance of pallidal reactions on thalamic stimulation.

3. Possible implications of these findings for the physiopathology of the basal ganglia are discussed.

REFERENCES

COWAN, W. M. and POWELL, T. P. S. The projection of the midline and intralaminar nuclei of the thalamus of the rabbit. *J. Neurol. Neurosurg. Psychiat.*, **1955**, *18*: 266-279.

DEMPSEY, E. W. and MORISON, R. S. The electrical activity of a thalamo-cortical relay system. *Amer. J. Physiol.*, **1943**, *138*: 283.

DROOGLEEVER-FORTUYN, J. and STEVENS, R. On the anatomical relations of the intralaminar and midline cells of the thalamus. *EEG Clin. Neurophysiol.*, **1951**, *3*: 393-398.

HASSLER, R. Uber die Rinden- und Stammhirnanteile des menschlichen Thalamus. *Psychiat. Neurol. mediz. Psychol.*, **1949**, *1*: 181-187.

GLEES, P. and WALL, P. D. Fibre connections of the subthalamic region and the centromedian nucleus of the thalamus. *Brain*, **1946**, *69*: 195-208.

KUHLENBECK, H. *The Human Diencephalon.* S. Karger, Basel — New York, **1954**.

MCLARDY, R. Projection of the centromedian nucleus of the human thalamus. *Brain*, **1948**, *71*: 290-303.

METTLER, F. Fiber connections of the corpus striatum of the monkey and baboon. *J. Comp. Neurol.*, **1945**, *82*: 169-204.

NASHOLD, B. S., HANBERY, J. and OLSZEWSKI, J. Observation on the diffuse thalamic projections. *EEG Clin. Neurophysiol.*, **1955**, *7*: 609-620.

POWELL, T. P. S. and COWAN, W. M. The connections of the midline and intralaminar nuclei of the thalamus of the rat. *J. Anat.*, **1954**, *88*: 307-319.

RANSON, S. W. and RANSON, S. W. JR. Efferent fibers of the corpus striatum. *Res. Publ. Ass. nerv. ment. Dis.*, **1942**, *21*: 69-76.

SACHS, E. On the structure and functional relations of the optic thalamus. *Brain*, **1909**, *32*: 95-186.

SPIEGEL, E. A. *Die Kerne im Vorderhirn der Säuger.* Arbeiten Neurol. Instit. Univ. of Vienna, **1919**, *22*: 418-497.

SPIEGEL, E. A. and WYCIS, H. T. Ansotomy in paralysis agitans. *Arch. Neurol. Psychiat.*, Chicago, **1954**, *71*: 598-614.

SPIEGEL, E. A. and WYCIS, H. T. Stimulation of brain stem and basal ganglia in man: in *Symposium on Brain Stimulation.* Univ. of Houston and Hogg Foundation, April, **1956** (in print).

STARZL, T. E. and MAGOUN, H. W. Organization of the diffuse thalamic projection system. *J. Neurophysiol.*, **1951**, *14*: 133-146.

STARZL, T. E. and WHITLOCK, D. G. Diffuse thalamic projection system of the monkey. *J. Neurophysiol.*, **1952**, *15*: 449-468.

VERZEANO, M., LINDSLEY, D. B. and MAGOUN, H. W. Nature of the recruiting response. *J. Neurophysiol.*, **1953**, *16*: 183-195.

VOGT, C. and VOGT, O. Thalamus Studien I-III. *J. f. Psychol. Neurol.*, **1941**, *50*: 32-154.

WALKER, A. E. *The Primate Thalamus.* University of Chicago Press, Chicago, **1938**.

Reference: SPIEGEL, E. A., SZEKELY, E. G. and BAKER, W. W. Electrographic study of thalamic impulses to the striatum and pallidum. *EEG Clin. Neurophysiol.*, **1957**, *9*: 291-299.

PRINTED IN CANADA

ANNOUNCEMENT

TRAINING GRANTS IN PSYCHIATRY

Psychiatric Resident appointments are available at Saint Elizabeths Hospital, Washington, D. C., to graduates of Canadian medical schools that are approved by the American Medical Association. Such graduates must have served an internship, either in Canada or the United States, that has been approved by the American Medical Association. Appointments may be made to other than American citizens in certain circumstances. The stipend is $3700, $4100, and $4500 for the first, second, and third year, respectively. Single rooms are available in the Hospital for $10 per month. Meals can be purchased at the Hospital cafeteria for up to $2.05 per day.

The training program includes organized lectures and seminars and supervised experience in psychotherapy, as well as other accepted forms of treatment. The residency is fully approved.

Washington, D. C., offers many educational and cultural advantages. Staff appointments after completion of the residency are generally available. For full information and application forms, write to the Superintendent, Saint Elizabeths Hospital, Washington 20, D. C.

SUPRASYLVIAN AUDITORY RESPONSES IN THE CAT [1]

CESARE T. LOMBROSO, M.D. and JEROME K. MERLIS, M.D. [2]
Seizure Unit, Department of Pediatrics at Harvard Medical School, National Veterans Epilepsy Center and the Neuropsychiatry Service, Boston VA Hospital, Boston, Mass.

(Received for publication: September 26, 1956)

On the basis of physiologic and histologic features, the classical ectosylvian auditory area is now considered to consist of three portions: A1, A2 and Ep. (Ades 1943; Bremer 1952; Lilly and Cherry 1952; Perl and Casby 1954; Rose 1949; Rose and Woolsey 1949; Woolsey and Walzl 1942). Tunturi (1945) has described an additional area, A3, in the ventral portion of the anterior ectosylvian gyrus in the dog, and similar observations in the cat have been made by Mickle and Ades (1952) and Bremer (1952) for an area comprising the inferior portions of the anterior ectosylvian and suprasylvian gyri and gyrus compositus (fig. 1). Our studies of the suprasylvian region in the cat have presented evidence for still another area responding to acoustic stimulation, distinct from the areas previously described, and manifesting certain features of interest.

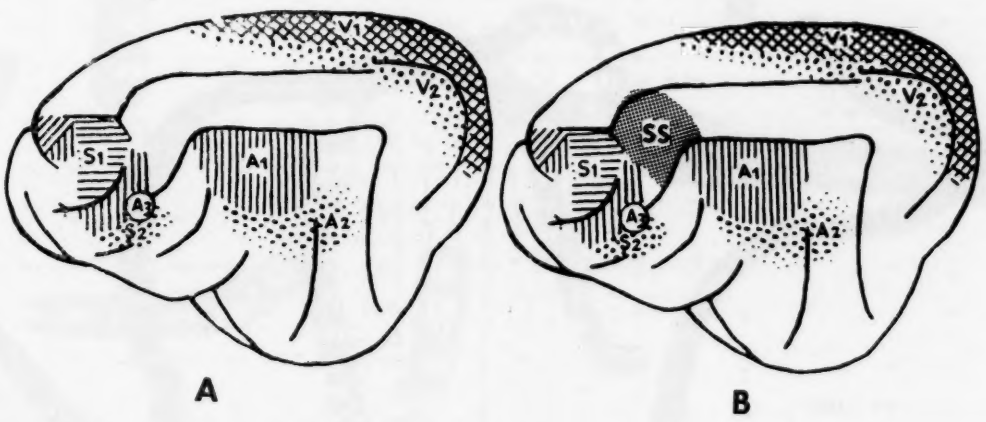


Fig. 1

A. Sensory areas of cat (after Bremer 1952).
AI, A2, A3 — auditory areas.
S1, S2 — somatosensory areas.
VI, V2 — Visual areas.
Ep is not designated.
B. To show SS — suprasylvian area of this communication.

METHODS

The observations were made on 32 adult cats. Anesthesia was induced by Nembutal (35-50 mg/kg.) or Dial-urethane (50-60 mg/kg.) intraperitoneally, supplemented by small increments intravenously as required. In some experiments unanesthetized curarized preparations and "encéphale isolé" preparations of Bremer were prepared under ether anesthesia and local procaine infiltration, and studied under artificial respiration. The cortex was exposed and kept moist and, in long-lasting experiments, was covered by a layer of warm mineral oil. Recording was accomplished through saline-wick electrodes leading to a Grass ink-writing oscillograph or

[1] This investigation was supported in part by a research grant, No. RG-3705(C2S), from The National Institute of Neurological Diseases and Blindness of The National Institute of Health, the U. S. Public Health Service.

[2] Now at University Hospital, Baltimore, Md.

to a double-beam Dumont cathode-ray oscilloscope. Recording was usually monopolar, using the neck muscles, nasal skin or the Horsley-Clarke instrument as the reference point. Significant responses were checked by bipolar pick-up.

Click stimuli were provided by the square wave output of a Grass stimulator through

In some experiments cortical ablation was performed aseptically, and the animals were studied after a six-week to six-month interval.

In two experiments a detailed map was made. The exploring electrodes were moved by means of the electrode carrier of a Horsley-Clarke instrument, using 1 mm. coordinates. Ten or more responses from each point were

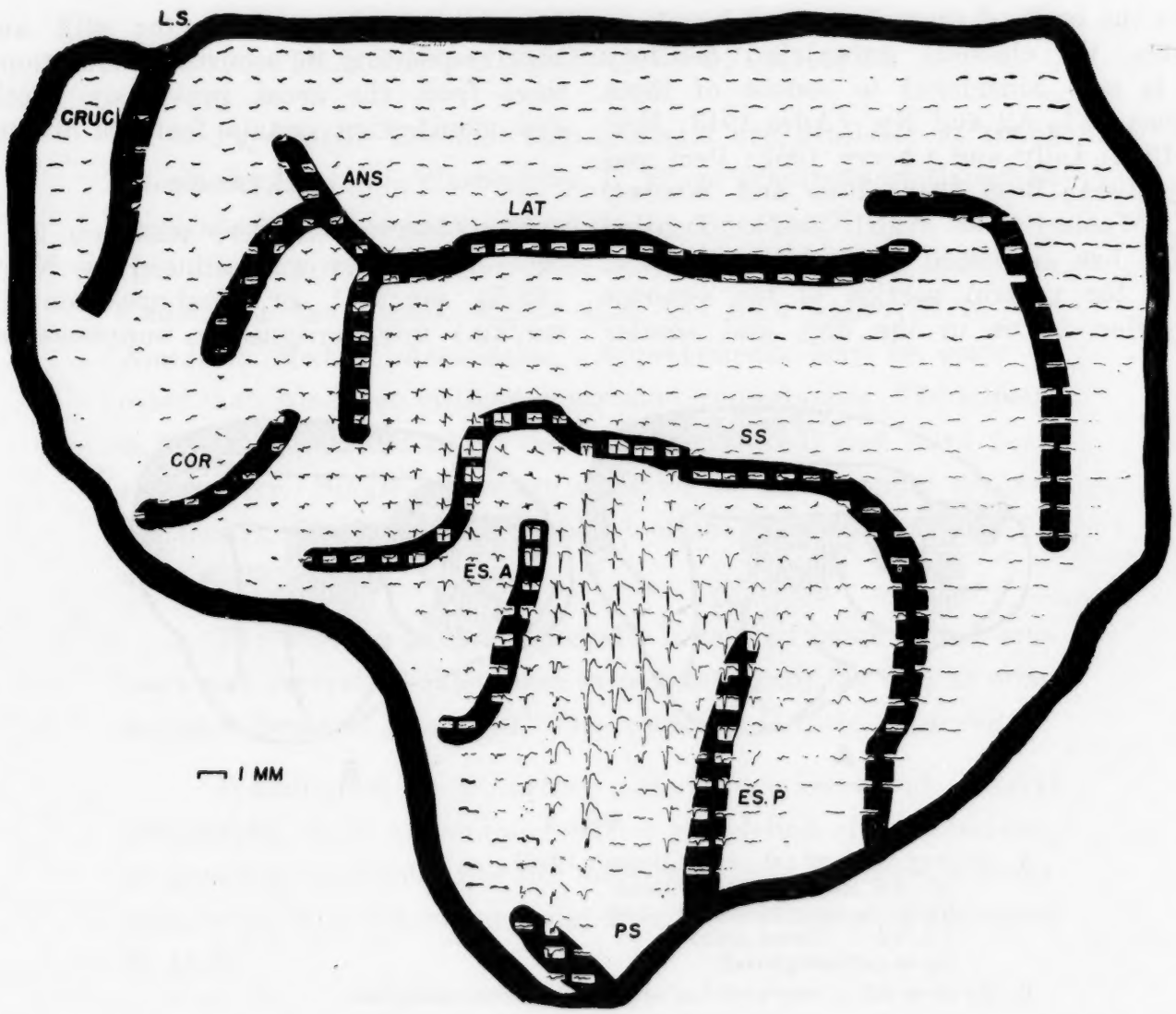


Fig. 2

Map of evoked responses to click, Dial anesthesia.

ear phones (PDR 8) or a loud speaker, the click being conducted either through air or through plastic tubing to one or both ears. The tube length was such as to interpose a 1 msec. delay between earphone response and the arrival of the sound at the ear. No attempt was made to explore intensity effects in any detail, a click of moderate intensity being used.

recorded from the cathode ray oscilloscope and enlarged scale maps of the consistent responses were prepared.

RESULTS

Figures 2 and 3 illustrate the results from an experiment in which approximately 1,000 sq. mm. of cortical surface were explored. Two areas of response to acoustic stimulation

are defined, one in the ectosylvian gyrus corresponding with A1 and A2 as described by others, and the other in the anterior suprasylvian gyrus lying more medially than the A3 area previously described (see fig. 1). In this experiment, the lower portion of the suprasylvian gyrus was not explored, and A3 is not defined, but other observations by areas there is usually a band of relatively unresponsive cortex. The wave form of the SS response consists of an initial large surface-positive deflection sometimes, but not always, followed by a slower negative deflection.

The anesthetic used, and its dosage, are of crucial significance in determining the limits of the responsive area. Under light to mod-

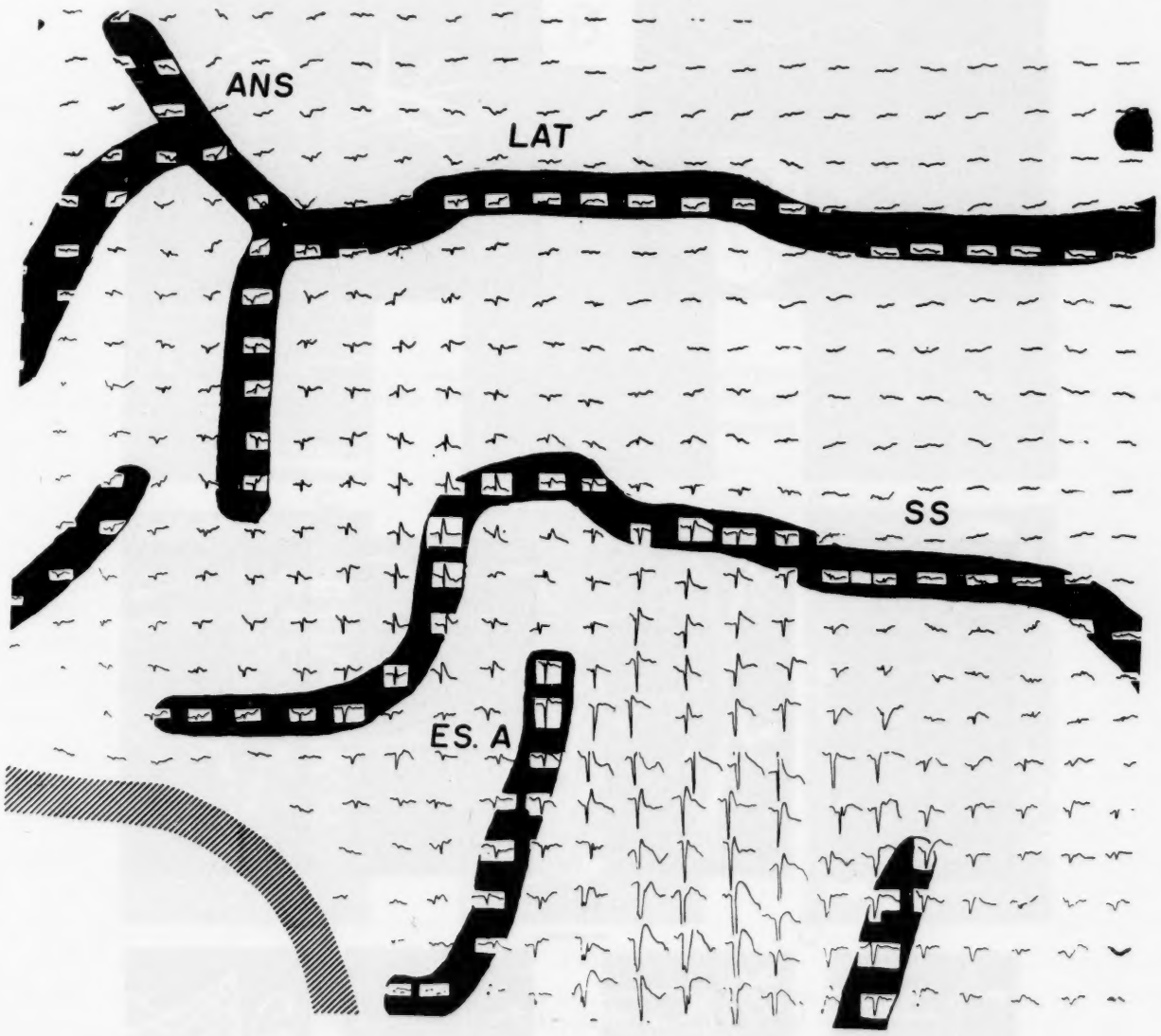


Fig. 3

Enlarged sector of map of figure 2.

us corroborate the localization of Mickle and Ades and of Bremer.

The anterior suprasylvian responses (SS) are usually of simpler wave form and lesser magnitude than those recorded from the ectosylvian gyrus (ES). Both respond approximately simultaneously with a latency of 5-8 msec., with neither consistently leading the other (fig. 4). Interposed between the two

erate Nembutal anesthesia (35-45 mg/kg.) the responses are prominent in the ectosylvian gyrus. Although sometimes absent, they frequently may be recorded from the suprasylvian region as well. Under light Dial anesthesia (50 mg/kg.) the suprasylvian responses are far more consistent and stable than under Nembutal, and may be of considerable magnitude. The SS responses have also been record-

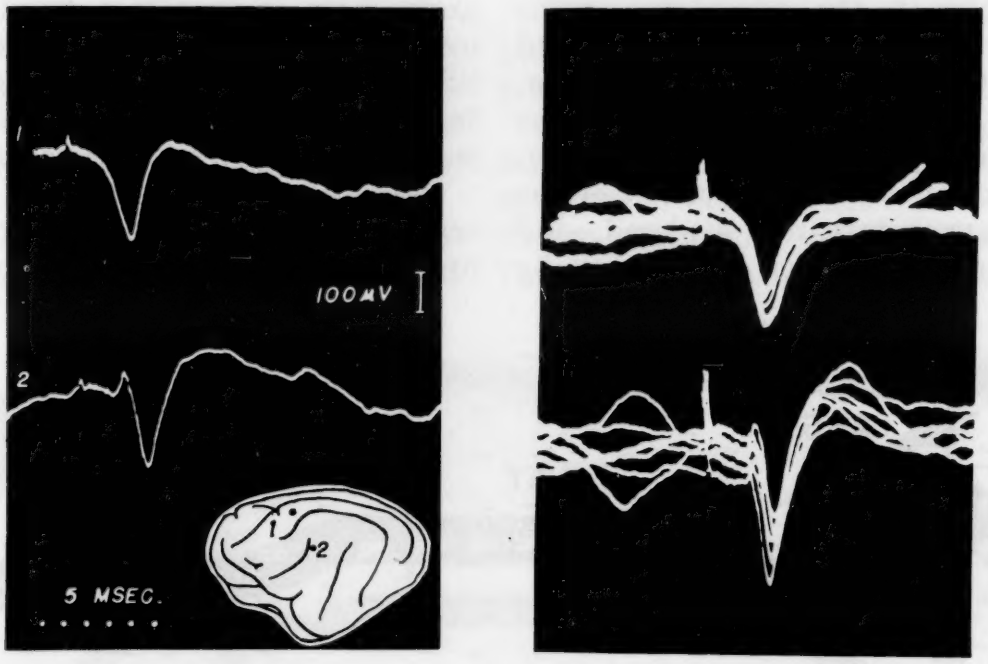


Fig. 4

Upper trace — suprasylvian response. Lower trace — ectosylvian response. Single and multiple responses. In this and in all other figures, negativity is signalled by an upward deflection.

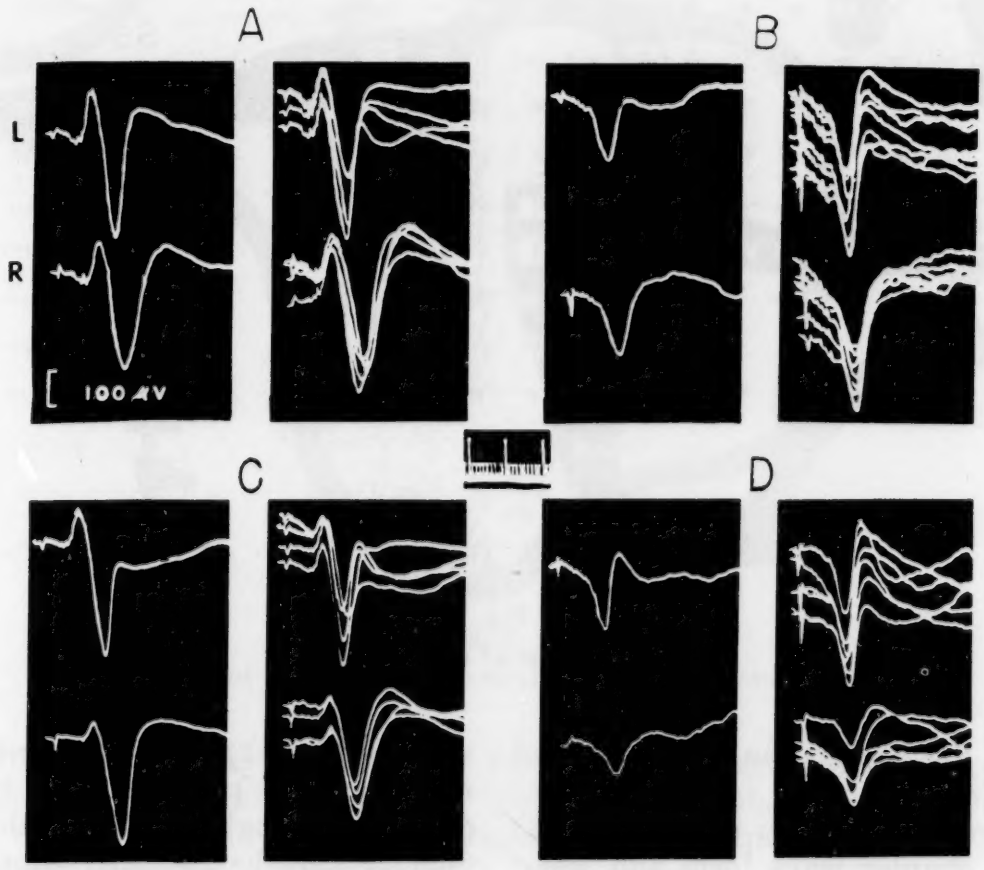


Fig. 5

A and C — ectosylvian and B and D — suprasylvian responses of the two hemispheres. Between B and C, left cochlea destroyed. Note marked attenuation of right SS response and augmentation, especially of negative phase, of left SS response. The right ES response shows slight attenuation. Time in msec (small divisions).

ed in the unanesthetized curarized animal and in the "encéphale isolé" preparation.

Increasing the depth of anesthesia with either Dial or Nembutal tends to abolish the SS response, whereas the ES response, although somewhat attenuated, is still easily obtained. In the unanesthetized curarized preparation, however, a small dose of Dial (3-5 mg/kg. i.v.) has produced immediate enhancement of the SS response.

The suprasylvian response does not depend upon the integrity of the ectosylvian area, for complete acute or chronic ablation of the ectosylvian gyrus, unilaterally or bilaterally, does not appreciably influence the responsiveness of the suprasylvian gyrus. Complete degeneration of the medial geniculate was not observed after such chronic ablation (see Rose and Woolsey 1949).

Augmentation of ES responses by the local application of strychnine (0.1-1.0 per cent) does not appreciably influence the SS responses, although spontaneous spiking is manifest in the strychninized ES area. In the usual preparation, the local application of strychnine to the SS area does not enhance the SS responses. However, under certain circumstances, as described below, a marked strychnine augmentation is demonstrable.

If completely monaural acoustic stimulation is achieved by destruction of one cochlea, the SS response of the contralateral hemisphere is depressed or abolished, although the ES response may be little affected (fig. 5).

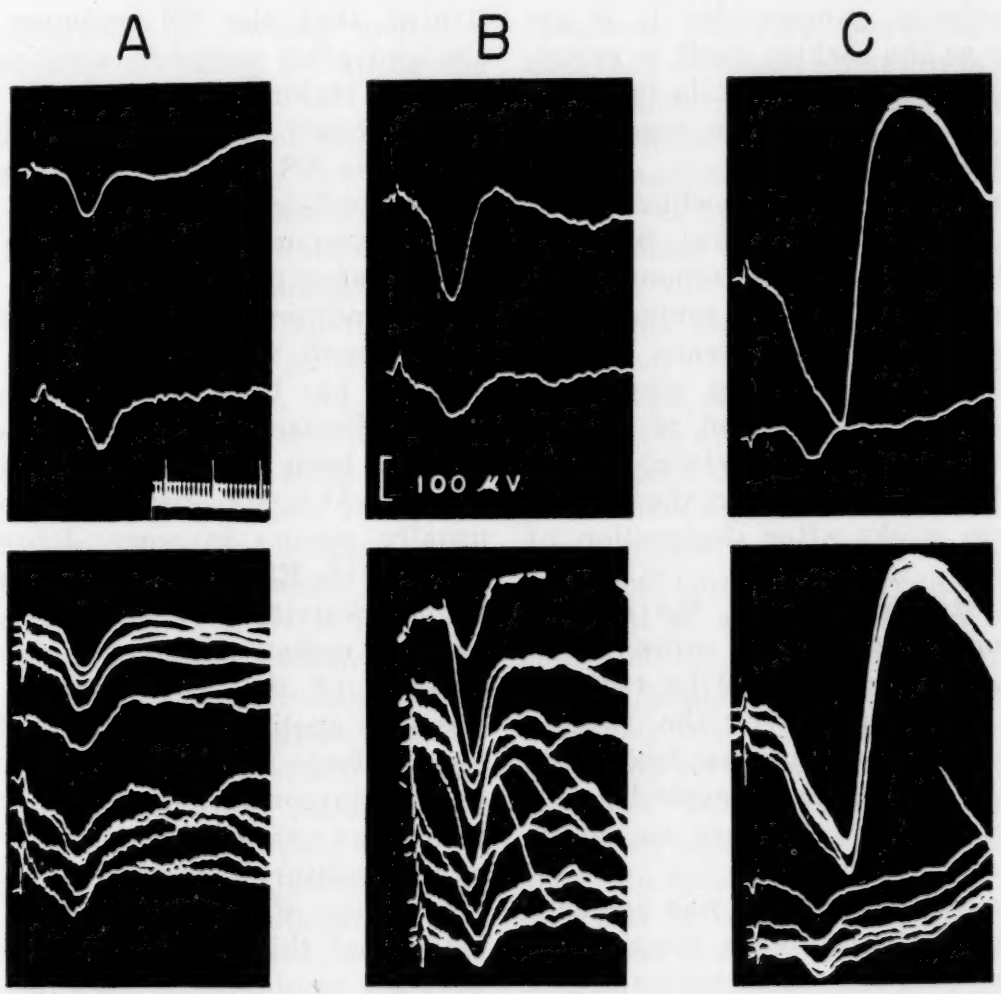


Fig. 6

Upper trace — left, and lower trace — right SS response.
A — after local application of strychnine to each SS area.
B — after destruction of left cochlea. Note augmentation of response on left.
C — after local application of strychnine to each SS area (left cochlea destroyed).

The ipsilateral SS response, on the other hand, usually is augmented, especially the surface-negative phase. We have noted that simply making a hole in the bulla frequently is sufficient to depress significantly the contralateral SS response. In association with Dr. Kiang (Massachusetts Institute of Technology) we have demonstrated that this depression is probably due to interference with the physical transmission process, for it is reversible so long as the cochlea itself is intact. Thus, if the hole made in the bulla is sealed with wax, the SS response again regains its previous amplitude.

After destruction of one cochlea, local strychninization of the ipsilateral SS area almost invariably augments its response (fig. 6). Strychnine applied to the contralateral SS area remains without influence on the responses, although spontaneous strychnine spikes appear. This phenomenon of strychnine augmentation of the suprasylvian evoked potential has also been observed in the chronic preparation, two weeks after destruction of one cochlea.

After local strychninization, the spontaneous strychnine spikes of either suprasylvian area are frequently accompanied by twitches of the pinna contralateral to the spiking cortex. This is also true, but less frequently so, of the strychnine augmented evoked potentials, which are usually of lower amplitude than the spontaneous spikes.

When monaural stimulation was achieved by applying the click through a plastic tube to one ear alone with the other cochlea intact, no consistent asymmetry of the SS responses was observed, nor was strychnine effective in augmenting the evoked SS responses.

DISCUSSION

Perl and Casby (1954), using the Laplacian electrode, failed to note any significant area of response to click in the suprasylvian region. In their experiments the anesthesia was moderate to deep sodium pentobarbital, as judged by areflexia and respiratory rate. Their studies have indicated a more restricted distribution of the acoustically evoked potential than is recorded with the usual monopolar or bipolar technique. They considered that the larger area of response with conventional methods of recording is due to passive spread from more distantly located active regions. Some doubt, then, may be placed on the interpretation that the potentials we have recorded from the suprasylvian region are truly evoked cortical responses.

Any such passive spread must arise from subcortical activity, since it is demonstrated that the SS response persists unchanged after complete ablation of the ectosylvian region. Inasmuch as the ES and SS responses are essentially identical in latency, the SS response is not a reflection of the geniculate response, which precedes the cortical response.

The most probable source of spread would be the auditory radiation volley. Indeed, the initial small negativity of the ES response (fig. 4) has been attributed to the afferent volley (Bremer 1952). Such an initial phase has not been observed by us in the SS response. Although destruction of one cochlea usually results in some depression of this phase of the ES response, and sometimes of the first positivity (a smaller response to a smaller radiation volley), the marked depression of the SS response, sometimes to complete abolition, quantitatively far exceeds these effects on the ES response. It is necessary to consider that the SS response is, to a large extent, dependent on the fraction of the auditory radiation volley abolished by destruction of the contralateral cochlea. The belief that this is so is supported by the depression produced by making a hole in the bulla. It is reasonable to assume that there is a direct relationship between the SS response and this specific portion of the auditory radiation volley, i.e. that this portion of the volley *evokes* the response rather than that this fraction of the volley passively contributes the potential to the SS area.

More crucial evidence furthering the interpretation of the SS response as a local cortical phenomenon is found in the results of the strychnine experiments. Although the failure of local strychnine to augment the SS response is not explained, similar failures have been noted for callosal volleys to the suprasylvian gyrus by Chang (1953) and callosal volleys to A1 and A2 by Bremer (1952).

The latter considers that this failure is due to a feeble synaptic density in the area strychninized.

The mechanisms involved in the increased sensitivity to local strychninization of the suprasylvian area after destruction of the ipsilateral cochlea require further investigation. It is of significance, however, that the evoked responses are augmented, and therefore must be responses of cortical neurones activated by an afferent volley set up by the click stimulus.

The functional significance of the various auditory areas which have been described is not clear. In the cat, total ablation of the ectosylvian A1 and A2 areas does not appreciably affect frequency discrimination, although when combined with S2 ablation (including A3), there is a deficit of minor degree (Meyer and Woolsey 1952). A1, A2 and Ep ablation does not produce deafness, but does produce loss of ability for tonal pattern discrimination (Diamond and Neff 1953). It is clear that removal of all the temporal lobe in the cat bilaterally does not abolish hearing.

A3 is an area in which there is an overlap of evoked potentials from auditory, vestibular, tactile and muscle stimulation, and it has been considered to represent an area for integration of impulses for postural adjustment and spatial orientation (Mickle and Ades 1952). One might anticipate that vision, so important in such adjustment and orientation, would have representation in this region, but we have not been able to demonstrate evoked response to flash in this region.

Pribram, Rosner and Rosenblith (1954) recently have described extratemporal auditory responses in the monkey, with significant responses in the parietal operculum. These responses persisted after acute ablation of temporal auditory cortex but not after chronic ablation. In this regard the findings differ from our observations in the cat, for in our experiments the SS response is not affected by chronic ablation of the ectosylvian auditory area. Although the homologue of cat's suprasylvian area in the monkey is not clear, it may well be represented in the parietal cortex (Kappers, Huber and Crosby 1936).

In the present study the augmentation of the SS response after destruction of the ipsilateral cochlea suggests that the cochlea exerts a significant tonic inhibitory influence on the ipsilateral response, whereas its excitatory influence is largely contralateral. The site of this inhibitory influence is not known, and further study of the phenomenon is required.

In another communication (Merlis and Lombroso 1955) we have reported the observation that electrical stimulation of the SS area of one hemisphere evokes pinna movement, at low threshold, limited to the contralateral ear, and sometimes, conjugate movement of the eyes to the opposite side. Stimulation of ES, on the other hand, evokes bilateral ear movement.

It has been pointed out (Bremer 1953) that areas of sensory-motor overlap subserve, at the least, simple cortical reflexes. Considering the SS area as one sensory-motor overlap, the pattern of reaction would be as follows: sound striking one ear more strongly than the other evokes a greater response in the contralateral suprasylvian region, the motor concomitant of which is the pricking up of the contralateral ear; i.e., the pinna of the ear more strongly stimulated acoustically. Simultaneously with this, the eyes, and perhaps the head may turn toward the site of origin of the stimulus. In contrast with this, the ectosylvian area pattern would be considered one to alert the animal to a stimulus not localizable in space, by causing both ears to prick up in a general reaction of attention.

The mechanism of the ability to localize sound in space is far from clear, although there is electrophysiologic evidence suggesting that unequal activation of A1 and A2 may be involved (Rosenzweig 1954). Neff *et al.* (1950) have indicated that bilateral ablation of A1 and A2 produces a severe deficit in a learned habit involving localization, although some degree of localization ability remains. The marked dependence of the SS response area on contralateral acoustic stimulation suggests that it may play a role in this mechanism.

SUMMARY

1. In the cat, auditory stimulation by click evokes potentials in an area of the anterior

suprasylvian gyrus distinct from areas previously described.

2. The suprasylvian response (SS) is not abolished by complete ablation of the ectosylvian gyri, bilaterally.

3. Augmentation of the ectosylvian response (ES) by local strychninization does not augment the suprasylvian response.

4. Destruction of one cochlea produces depression of the contralateral SS response and augmentation of the ipsilateral SS response.

5. Locally applied strychnine does not influence the SS response when both cochleas are intact. After destruction of one cochlea, local strychninization augments the ipsilateral SS response.

6. The SS response area is coextensive with the area in which electrical stimulation evokes movements of the contralateral pinna and conjugate deviation of the eyes to the opposite side. It is considered that this is an area of sensory-motor overlap subserving a cortical reflex for oriented alerting to sound localized in space.

REFERENCES

ADES, H. W. A secondary acoustic area in the cerebral cortex of the cat. *J. Neurophysiol.*, **1943**, *6*: 59-64.

BREMER, F. Analyse oscillographique des réponses sensorielles des écorces cérébrale et cérébelleuse. *Rev. Neurol.*, **1952**, *87*: 65-92.

BREMER, F. *Some Problems in Neurophysiology*, London, The Athlone Press, **1953**.

CHANG, H. T. Similarity in action between curare and strychnine on cortical neurones. *J. Neurophysiol.*, **1953**, *16*: 221-233.

DIAMOND, I. T. and NEFF, W. D. Role of auditory cortex in discrimination of tonal pattern. *Fed. Proc.*, **1953**, *12*: 33.

KAPPERS, C. U. A., HUBER, G. C. and CROSBY, E. C. *The Comparative Anatomy of the Nervous System of Vertebrates Including Man.* New York, The Macmillan Co., **1936**.

LILLY, J. C. and CHERRY, R. New criteria for the division of the acoustic cortex into functional areas. *Fed. Proc.*, **1952**, *11*: 94.

MERLIS, J. K. and LOMBROSO, C. T. Cortically-evoked pinna movement in the cat. *Proc. Soc. Exp. Biol. Med.*, **1955**, *90*: 577-580.

MEYER, D. R. and WOOLSEY, C. N. Effects of localized cortical destruction on auditory discriminative conditioning in the cat. *J. Neurophysiol.*, **1952**, *15*: 149-162.

MICKLE, W. A. and ADES, H. W. A composite sensory projection area in the cerebral cortex of the cat. *Amer. J. Physiol.*, **1952**, *170*: 682-689.

NEFF, W. D., ARNOTT, G. P. and FISHER, J. D. Function of the auditory cortex: localization of sound in space. *Amer. J. Physiol.*, **1950**, *163*: 738.

PERL, E. R. and CASBY, J. V. Localization of cerebral electrical activity: the acoustic cortex of the cat. *J. Neurophysiol.*, **1954**, *17*: 429-442.

PRIBRAM, K. H., ROSNER, B. S. and ROSENBLITH, W. A. Electrical responses to acoustic clicks in monkey: extent of neocortex activated. *J. Neurophysiol.*, **1954**, *17*: 336-344.

ROSE, J. E. The cellular structure of the auditory region of the cat. *J. Comp. Neurol.*, **1949**, *91*: 409-440.

ROSE, J. E. and WOOLSEY, C. N. Relations of thalamic connections, cellular structure and evocable electrical activity in the auditory region of the cat. *J. Comp. Neurol.*, **1949**, *91*: 441-466.

ROSENZWEIG, M. R. Cortical correlates of auditory localization and of related perceptual phenomena. *J. Comp. Physiol. Psychol.*, **1954**, *47*: 269-276.

TUNTURI, A. R. Further afferent connections to the acoustic cortex of the dog. *Amer. J. Physiol.*, **1945**, *144*: 389-394.

WOOLSEY, C. N. and WALZL, E. M. Topical projection of nerve fibers from local regions of the cochlea to the cerebral cortex of the cat. *Bull. J. Hopkins Hosp.*, **1942**, *71*: 315-344.

Reference: LOMBROSO, C. T. and MERLIS, J. K. Suprasylvian auditory responses in the cat. *EEG Clin. Neurophysiol.*, **1957**, *9*: 301-308.

PRINTED IN CANADA

THE ENTORHINAL AREA; ELECTROPHYSIOLOGICAL STUDIES OF ITS INTERRELATIONS WITH RHINENCEPHALIC STRUCTURES AND THE BRAINSTEM [1]

W. R. Adey, M.D., S. Sunderland, M.D. and C. W. Dunlop, M.Sc.
Department of Anatomy, University of Melbourne, Australia

(Received for publication: August 9, 1956)

That part of the cerebral cortex of the mammalian temporal lobe lying medial to the rhinal sulcus and forming the hippocampal gyrus can be divided into two portions. The anterior or prepyriform zone covers the more deeply placed amygdaloid nuclei. This prepyriform portion of the hippocampal gyrus has been shown anatomically and physiologically to be primarily concerned in olfactory functions (Rose and Woolsey 1943; Le Gros Clark and Meyer 1947; Meyer and Allison 1949; Kaada 1951; Adey 1953). The larger posterior portion of the hippocampal gyrus was described by Brodmann (1909) as the entorhinal area, and by Cajal (1911) as "l'écorce temporale postérieure ou supérieure".

Little is known of the connexions of the entorhinal area. Anatomical evidence has suggested that it forms a major source of afferent fibres to the hippocampus through the temporo-ammonic tracts (Cajal 1911; Lorente de Nó 1934; Adey and Meyer 1952). It was suggested by Papez (1937) that these connexions formed part of a reentrant pathway concerned with emotional activity and running from entorhinal area to hippocampus, thence via the fornix to the mammillary bodies and so to the anterior thalamic nuclei where a further relay would carry the impulses to the cingulate gyrus. Activity would ultimately return to the entorhinal area via the cingulum bundles.

More recently experimental evidence has been advanced for the existence of pathways proceeding to the hippocampus and entorhinal area in a direction opposite to that suggested in the Papez circuit. Degenerating fibers running in a caudal direction follow transection of the fornix in the guinea pig (Morin 1950). No retrograde cell degeneration in the hippocampal pyramids follows transection of the fornix (Daitz and Powell 1954; McLardy 1955a). Stimulation of the fornix is followed by discharges in the hippocampus, and the available evidence suggests that this conduction represents true orthodromic conduction in fornix fibers (Green and Shimamoto 1953; Green and Arduini 1954; Liberson and Akert 1955; Green and Adey 1955, 1956).

An afferent pathway to the hippocampus through the fornix can be activated by stimulation of many zones in the upper midbrain, thalamus and septum, including those regions forming part of a "non-specific" cortical afferent system (French, Amerongen and Magoun 1952). The regular slow-wave discharge seen in the hippocampus from both peripheral sensory stimulation and electrical stimuli delivered directly to the central regions of the diencephalon suggests that the fornix may form a pathway to rhinencephalic structures including the hippocampus and that these in turn may play a part in mechanisms of "alerting" and "arousal".

Recent electrophysiological and histological studies of efferent connexions of the entorhinal area (Adey, Segundo and Livingston 1955; Adey, Merrillees and Sunderland 1956) have indicated an extensive caudally directed pathway running from the entorhinal area to the dorsal midbrain tegmentum through the stria medullaris. Interruption of this pathway by removal of the entorhinal area in the marsupial phalanger is followed by profound alteration in the emotional responses to provocation.

[1] This work was assisted by grants from the National Health and Medical Research Council of Australia.

The evidence thus suggests that the hippocampus may be accessible to afferent paths from both the fornix and the entorhinal area. We have endeavoured in the present study to determine the patterns of integration occurring in the hippocampus and enthorhinal area from stimulation at closely spaced intervals of two or more points within these regions. Latency studies in the stria medullaris and dorsal tegmentum of the midbrain have afforded evidence in support of a caudally directed outflow from the hippocampus through the entorhinal area to the central regions of the midbrain.

MATERIAL AND METHODS

Sixteen specimens of the marsupial phalanger (*Trichosurus vulpecula*) have been used in the present study. In all experiments ether anesthesia was discontinued after exposure of the brain and infiltration of the scalp with 2 per cent procaine hydrochloride solution; d-tubocurarine in a single dose of 5 mg. was administered by the intraperitoneal route. The trachea was cannulated in all experiments and the parameters of artificial respiration were controlled electronically. Particular care was taken to avoid hyperventilation. An interval of at least one hour was allowed in all experiments after cessation of ether anesthesia before the commencement of rhinencephalic explorations.

Stimulating and recording electrodes were of identical construction. Concentric electrodes were used, having an insulated stainless steel barrel (24 SWG) and an insulated stainless steel central wire (32 SWG) projecting slightly beyond the tip of the barrel. Bipolar records were obtained between the bared tips of the barrel and the central conductor. Monopolar records were taken between the central conductor and a point on the adjacent scalp.

The recording system used twin amplifiers, each consisting of a Tektronix type 122 preamplifier driving a main amplifier, the overall frequency response being uniform between 1 c/sec. and 15 kc/sec. In the majority of experiments bipolar and monopolar records from the same point were displayed simultaneously on a double-beam cathode-ray tube. Square-wave stimuli were obtained from a pair of Grass stimulators equipped with isolation units.

Electrodes were inserted stereotaxically with the aid of a Lab-tronics stereotaxic instrument. In this animal the entorhinal area is so disposed that a considerable portion (about 7 mm.) of its length can be explored by a vertically directed electrode. At the conclusion of all experiments the brain was removed and fixed in 10 per cent formalin in normal saline. The disposition of electrode tracks was subsequently determined from serial Nissl sections cut frozen at a thickness of 40 μ.

RESULTS

1. *Records from fornix, hippocampus and entorhinal area during stimulation of either fornix or entorhinal area.*

In view of the possibility that, in addition to the pathways classically described as running from entorhinal area to hippocampus and thence to fornix, a flow of impulses might occur in the opposite direction, initial experiments were directed to testing the extent and reciprocity of these paths.

(*a*) *Records from hippocampus and fornix during stimulation of the entorhinal area.*

Recording electrodes were inserted into the dorsal hippocampus in the junctional region between the layer of hippocampal pyramids and the adjoining cap of dentate pyramidal cells (the region CA4 of Lorente de Nó). The electrode in the fornix was placed in the fornix commissure about 2 mm. from the midline. The electrode in the entorhinal area was placed in the deeper cortical layers at a level corresponding approximately to the middle of the vertical extent of this strip of cortex.

Single shocks (7.0 V., 1.0 msec.) applied to the entorhinal electrode were always followed by a response in the dorsal hippocampus. These responses were biphasic in bipolar records with an initial deflection lasting 30 msec. followed by a longer component about 80 msec. in duration and of opposite polarity to the initial deflection. Repetitive stimulation of the entorhinal area (3 per sec., 6.5 V., 1.0 msec.) did not significantly modify the hippocampal response.

Simultaneous records from the fornix failed to reveal a significant response to entorhinal stimulation (fig. 1-B). Many records showed no response at all, and those which did showed merely a slow wave of low amplitude and approximately synchronous with the slower component of the hippocampal response. No response was seen in the fornix corresponding to the initial component of the hippocampal response.

(*b*) *Records from the hippocampus and entorhinal area during stimulation of the fornix.*

In the course of the experiments described in (*a*), stimuli were applied to the fornix entorhinal area, and in both the initial deflection in bipolar records showed a more rapid early phase than that seen in the hippocampus from entorhinal stimulation, lasting only about 20 msec. The ensuing slow wave deflection of opposite polarity lasted 80-150 msec. Rolling film records following single shocks to the fornix indicated a complex series of slow waves in the hippocampus for several seconds after the primary response, but these were not as well sustained in the simultaneous record from the entorhinal area (fig. 1-C).

Thus, in summary, stimulation of the fornix was followed in the hippocampus by large responses which were also recorded readily

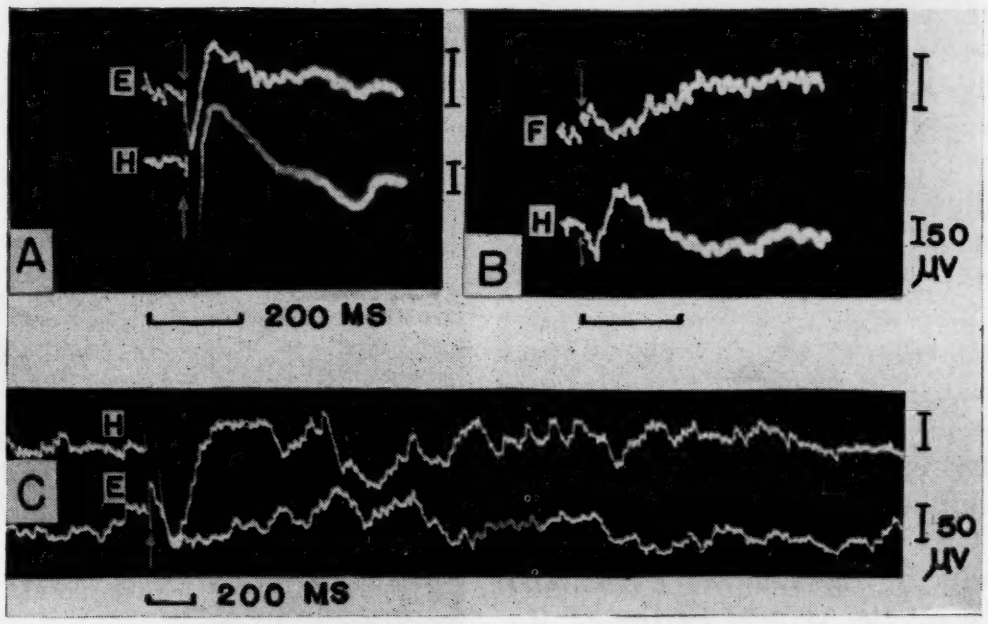


Fig. 1

A and B. Tests of reciprocity of conduction between fornix, hippocampus and entorhinal area. A, stimulation of fornix (7.5 V., 0.5 msec.) while recording in the hippocampus (H) and entorhinal area (E). B, stimulation of entorhinal area (6.5 V., 1.0 msec.) while recording in the hippocampus (H) and fornix (F). There is only a minimal response in the fornix to entorhinal stimulation. C, simultaneous records from hippocampus (H) and entorhinal area (E) during stimulation of the fornix (7.0 V., 0.5 msec.). Rhythmic slow-wave trains appear longer sustained in the hippocampus than in the entorhinal area. Bipolar records.

while recording from the hippocampus and entorhinal area. It is emphasized that no changes were made in the disposition of any of the three electrodes between stimulation of the entorhinal area and stimulation of the fornix in these experiments.

Single shocks to the fornix (7.5 V., 0.1-0.5 msec.) were constantly followed by large biphasic responses in both the hippocampus and in the entorhinal area. On the other hand, stimulation of the entorhinal area was followed by smaller responses in the hippocampus, and rarely by a response in the fornix.

2. *Records from the hippocampus during delivery of paired shocks to the fornix and entorhinal area.*

It was obvious that, in addition to varying interaction patterns at differing shock spac-

ings, changes in interaction patterns might be expected during progressive penetration of the hippocampal formation. It was found that examination of 6 to 8 representative shock spacings at each hippocampal level while progressing in 0.5 mm. steps afforded a fairly comprehensive picture of the over-all interaction pattern.

It should be emphasized that while the results presented were those seen constantly in all experiments, and may be taken to indicate the general pattern of interaction, variations were noted in the extent of interaction at a particular point with a particular shock spacing. The procedure adopted was to stimulate the fornix 300, 200, 120 or 80 msec. before applying a test shock to the entorhinal area. The procedure was then reversed and conditioning shocks applied in the entorhinal area 300, 200, 120 or 80 msec. before a test shock to the fornix.

The recording electrode passed through the same region of the dorsal hippocampus in all experiments. It will be seen from the diagram (fig. 2) that the recording tip penetrated successively through the alveus, the layer of hippocampal pyramidal cells, the fibers of the perforant temporoammonic tract, the cells of the dentate gyrus, the terminal zone between hippocampal and dentate pyramids (area CA4 of Lorente de Nó), reentered the cells of the dentate gyrus and finally emerged on the ventral border of the hippocampus to penetrate the thalamus.

(*a*) *Stimulation of the fornix prior to stimulation of the entorhinal area.*

Under these conditions there was inhibition (presumably due to blocking interaction) of the response in the hippocampus to the test stimulus applied in the entorhinal area (fig. 3). The amount of inhibition varied in different parts of the hippocampus and in different experiments, but in all experiments there was evidence that stimulus spacings producing maximal inhibition varied at different depths in the hippocampus.

In this respect there was some evidence of a dorsoventral temporal gradient through the hippocampus, with inhibition occurring dorsally in the vicinity of the hippocampal pyramidal cells at shock spacings of 80 msec., and at gradually increasing spacings up to 300 msec. near the ventral surface of the

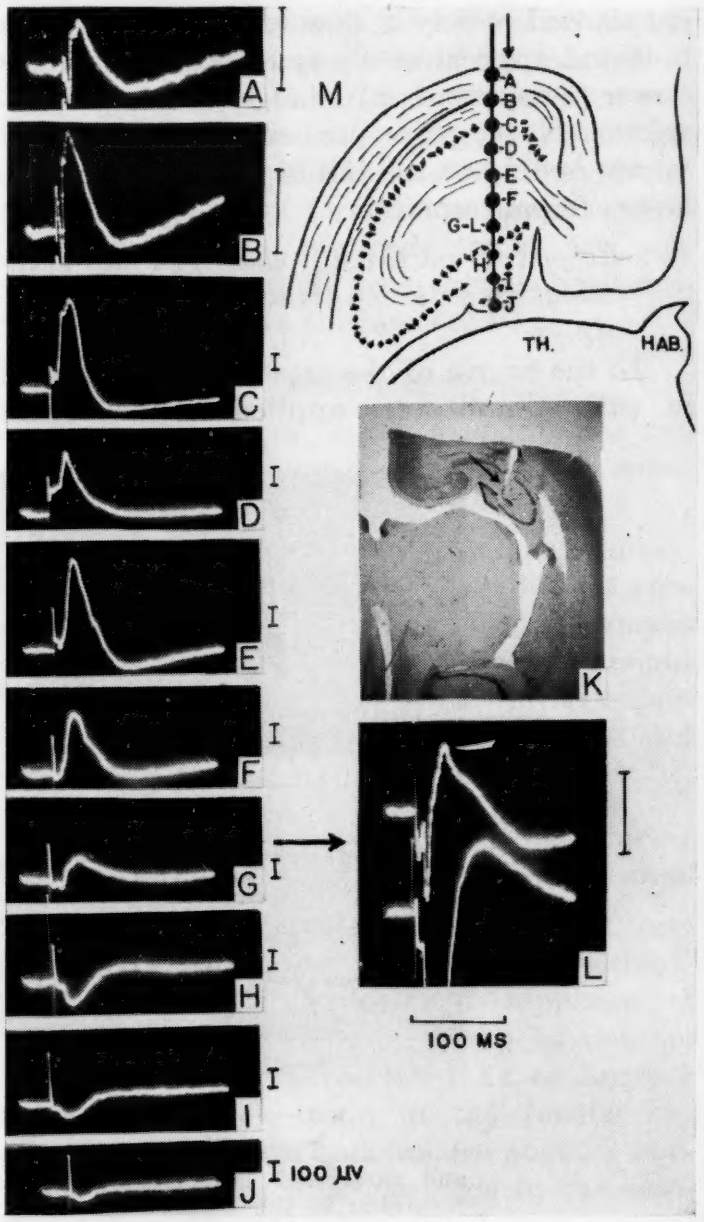


Fig. 2

Bipolar records from the hippocampus during its progressive penetration by the recording electrode. Records A to J, and including L, were taken in 0.5 mm. steps (as depicted in M) during stimulation of the fornix (7.0 V., 0.3 msec.). Amplifier gain was reduced between records B and C. Record L is from the same point as G but at the original amplifier gain setting to show the persistence of a small "presynaptic" component noted also in records A and B. A portion of a simultaneous monopolar record appears in the lower part of L. There is a phase reversal of the main deflection of the response between G and H in the vicinity of the dentate pyramidal cells. The photomicrograph K shows an electrode track with its tip in the region CA4 in which fixed hippocampal electrode tips were usually inserted. Abbreviations : TH, thalamus; HAB, habenular nucleus. All voltage calibrations, 100 μV.

hippocampus. With the electrodes used, no modification in this gradient could be detected as the recording tip traversed the region of the dentate pyramids, although in 4 of the 7 experiments in which the phenomenon was tested the amount of inhibition was greater in the region of the dentate pyramids than at either more superficial levels or nearer the ventral border of the hippocampus. This is of interest in view of the evidence of a "turn-over" in the hippocampal response to fornix stimulation in the vicinity of the dentate pyramids (vide infra).

increased by over 100 per cent. At closer shock spacings (80-120 msec.) a slight inhibition of the test response was also noted. No clear temporal gradient in the interaction patterns could be discerned at different depths in the hippocampus.

In two experiments a recording electrode was inserted into the ventral hippocampus, but owing to the absence of a satisfactory response to entorhinal stimulation, its interaction patterns could not be studied, although it responded strongly to stimulation of the fornix.

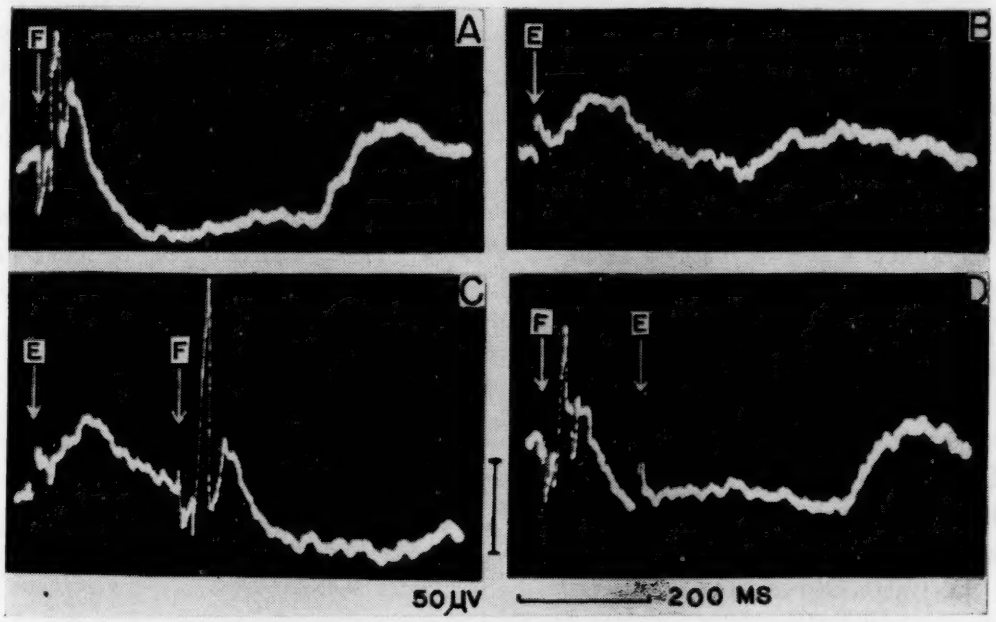


Fig. 3

Interaction patterns in the dorsal hippocampus. A, control response to fornix stimulation (6.0 V., 0.2 msec.). B, control response to entorhinal stimulation (7.0 V., 1.0 msec.). C, Facilitation of test response to fornix stimulation (F) by conditioning entorhinal stimulus (E). D, Inhibition of test response to entorhinal stimulation (E) by conditioning fornix stimulus (F). Bipolar records.

(*b*) *Stimulation of the entorhinal area prior to stimulation of the fornix.*

Under converse conditions of stimulation, with the stimulus to the entorhinal area preceding that to the fornix, rather different interaction patterns were seen in the hippocampal responses. Facilitation of the test response to fornix stimulation was found at all depths through the hippocampal formation, but occurred at greater shock spacings than in (*a*) and appeared maximal at spacings of 150-300 msec. (fig. 3). In some experiments this facilitation was considerable, both amplitude and duration of the response being

(*c*) *"Turn-over" points in hippocampal responses to fornix and entorhinal stimulation.*

Examination of the hippocampal responses during progressive penetration has indicated phase reversals which may be significantly related to the intrahippocampal course of certain fiber paths, or to patterns of polarization in sheets of linearly aggregated nerve cells. Bipolar and monopolar responses were recorded simultaneously, but the biggest changes were seen in the bipolar record.

It was found (fig. 2) that during progressive penetration of the hippocampus the

response to fornix stimulation increased rapidly in size over a distance of 1 mm. from the dorsal border of the hippocampus. The response in the bipolar record at this level (in the vicinity of the hippocampal pyramids) constantly showed an initial small rapid mono- or biphasic deflection, followed by a large biphasic response lasting about 50 msec. The first deflection of the large biphasic wave lasted 7-10 msec. and the second deflection about 40 msec. The large biphasic wave was succeeded by a long slow-wave lasting about 80 msec. and having the same polarity as the initial deflection of the large biphasic wave.

At depths between 1.5 and 2.0 mm. below the dorsal surface of the hippocampus the response decreased in size. Nevertheless the earliest phase of the response, the small rapid mono- or biphasic deflection, remained unaltered (fig. 2-L). At a depth of 2.5-3.0 mm. below the dorsal border of the hippocampus, in the vicinity of the dentate pyramidal cells, there was a phase reversal of the second part of the large biphasic response, and at the same level the long late slow-wave became very small. This modified response showed no further change up to the point where responses ceased at the ventral border of the hippocampus, 3.5 mm. below the point of initial penetration.

No comparable "turnover" points were seen in the hippocampal responses to stimulation of the entorhinal area. The hippocampal responses to entorhinal stimulation usually showed a greater degree of temporal dispersion than after fornix stimulation.

3. *Interrelationships between the entorhinal area and the dorsal and ventral portions of the hippocampus.*

(*a*) *General pattern of electrophysiological interrelations.*

Electrodes were inserted into fixed positions in the dorsal and ventral portions of the hippocampus, while a third electrode was moved in 1 mm. steps through the entorhinal area (fig. 4-A). In this way it was hoped to obtain information concerning possible regional projections from the entorhinal area to the hippocampus and vice versa at different levels in the entorhinal area, and also to study the interaction patterns in the entorhinal area to dorsal and ventral hippocampal stimuli.

The dorsal hippocampal electrode was inserted into area CA4 between the hippocampal and dentate pyramidal cells at level A9 of the Horsley-Clarke coordinates. The ventral hippocampal electrode was inserted into the same position relative to the hippocampal and dentate pyramids (fig. 4-B). It was considered that these electrode sites were sufficiently remote from alvear fibers on the hippocampal surface to obviate direct stimulation of, or pick-up from, these structures. From the many hundreds of evoked potential records certain general patterns in the projection paths were common to all experiments.

Stimulation of the dorsal hippocampus was uniformly followed by large responses at all depths in the entorhinal area. The responses remained relatively constant in

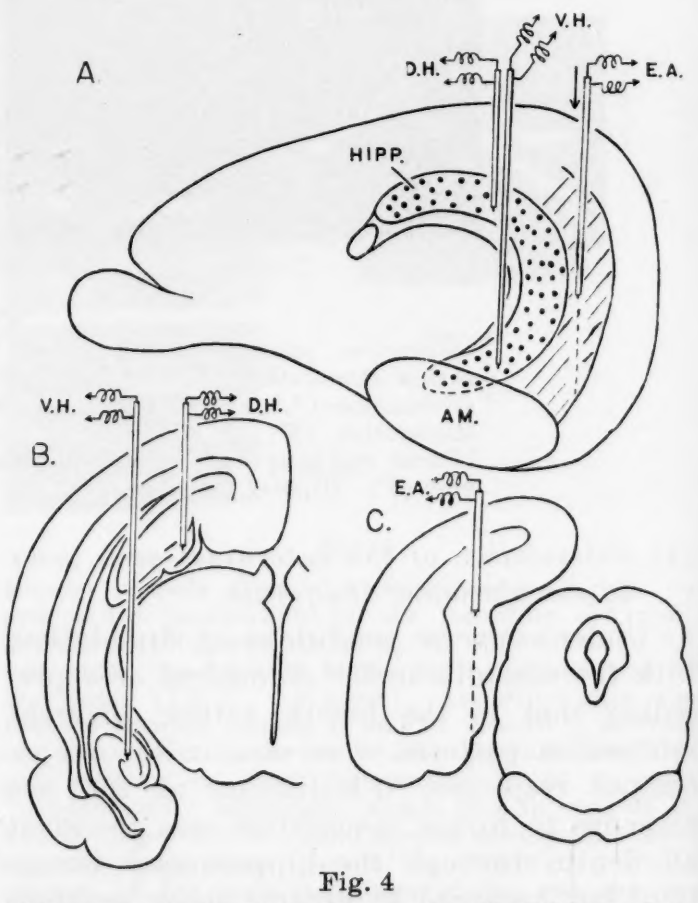


Fig. 4

Diagrammatic arrangement of the disposition of recording electrodes in dorsal hippocampus, ventral hippocampus and entorhinal area. Abbreviations: AM, amygdala; D.H., dorsal hippocampal electrode; E.A., entorhinal electrode; HIPP, hippocampus; V.H., ventral hippocampal electrode.

form from the junctional region between cingulate and entorhinal cortical areas dorsally to the junction of entorhinal and periamygdaloid cortex ventrally, a distance of about 8 mm. Typically there was an early biphasic response in which the initial deflection lasted 25-35 msec. and was followed by a slower component lasting two or three times as long. In many positions of the entorhinal electrode a small wave or notch preceded the main deflection of the initial biphasic response, and had many of the characters of a presynaptic spike. Under conditions of repetitive stimulation (3 per sec., 7 V., 0.1 msec.) the entorhinal response to dorsal hippocampal stimulation showed great recruitment, with differential facilitation of the various portions of the response (fig. 5-A). This recruitment could be elicited without difficulty even at the lower end of the entorhinal area.

Latency measurements in rhinencephalic structures in curarized preparations tend to be difficult, with response inflections concealed in a relatively high background of spontaneous activity. As far as could be determined, there was no significant latency gradient in the appearance of responses in the entorhinal area to dorsal hippocampal stimulation, responses at all depths having a latency of 7-10 msec.

In contrast to the large projections from the dorsal hippocampus to the entorhinal area, responses at each level in the entorhinal area to ventral hippocampal stimulation were usually smaller than those induced by dorsal hippocampal stimulation. Moreover, it was not always possible to record a response to ventral hippocampal stimulation in the dorsal parts of the entorhinal area. The results suggest more extensive connexions of the ventral hippocampus with the ventral portions of the entorhinal area, but even in the ventral part of the entorhinal area the responses were usually smaller than those from dorsal hippocampal stimulation. By contrast to stimulation of the dorsal hippocampus, recruitment of the entorhinal response to ventral hippocampal stimulation was much less pronounced (fig. 5-B). Latencies of the responses to ventral hippocampal stimulation were between

Fig. 5

Entorhinal responses to repetitive hippocampal stimulation. In A and B, upper trace is monopolar, lower trace is bipolar record. A, stimulation of dorsal hippocampus (7.0 V., 0.1 msec., 3 per sec.) with marked recruitment in responses at ventral end of entorhinal area. B, stimulation of the ventral hippocampus (9.0 V., 0.4 msec., 3 per sec.) without comparable recruitment of responses noted in A. C, stimulation of the ventral hippocampus (10.0 V., 0.5 msec., 10 per sec.) showing shortening of latency of entorhinal responses with consecutive stimuli. Bipolar record.

7-15 msec. and showed no significant differences in various parts of the entorhinal area. There was evidence of shortening latency during repetitive stimulation to considerably less than 10 msec. (fig. 5-C).

Stimulation of the entorhinal area during the progressive descent of an electrode through it also suggested some interesting differences in the extent of projections to dorsal and ventral regions of the hippocampus. Large responses were recorded in the dorsal hippocampus from stimulation of the entorhinal area at all levels down to the junctional region with periamygdaloid cortex, where they became abruptly smaller. Responses in the ventral hippocampus to stimulation of the entorhinal area were smaller than those in the dorsal hippocampus and less often followed by slow-wave complexes. They were not significantly augmented as the stimulating electrode approached the ventral zones of the entorhinal area.

It is of particular interest that large reciprocally conducting pathways were present between dorsal and ventral areas of the hippocampus, and between the ventral part of the entorhinal area and the dorsal hippocampus. Yet connexions in either direction between the ventral part of the entorhinal area and the adjacent ventral hippocampus appeared less significant, suggesting that the ventral entorhinal area and the ventral hippocampus may be independently connected with the dorsal hippocampus (fig. 9).

(*b*) *Interaction patterns in the entorhinal area to spaced single shocks in the dorsal and ventral regions of the hippocampus.*

A recording electrode was moved progressively through the entorhinal area in 1 mm. steps. At each level single conditioning shocks were applied 200 msec. before single test shocks to the ventral hippocampus. A further series of responses was recorded with the shock spacing reduced to 100 msec. The procedure was then reversed and conditioning stimuli applied to the ventral hippocampus either 200 or 100 msec. before a single test stimulus to the dorsal hippocampus. In both arrangements the effects were also tested of repetitive administration at 3 per sec. of paired shocks spaced 100 msec.

A conditioning stimulus in the dorsal hippocampus was found to powerfully inhibit the test response to ventral hippocampal stimulation at all depths of the entorhinal area, and at both 200 and 100 msec. shock spacing. This blocking interaction was also clearly observed during repetitive stimulation (fig. 6).

Interaction patterns following a conditioning stimulus in the ventral hippocampus and

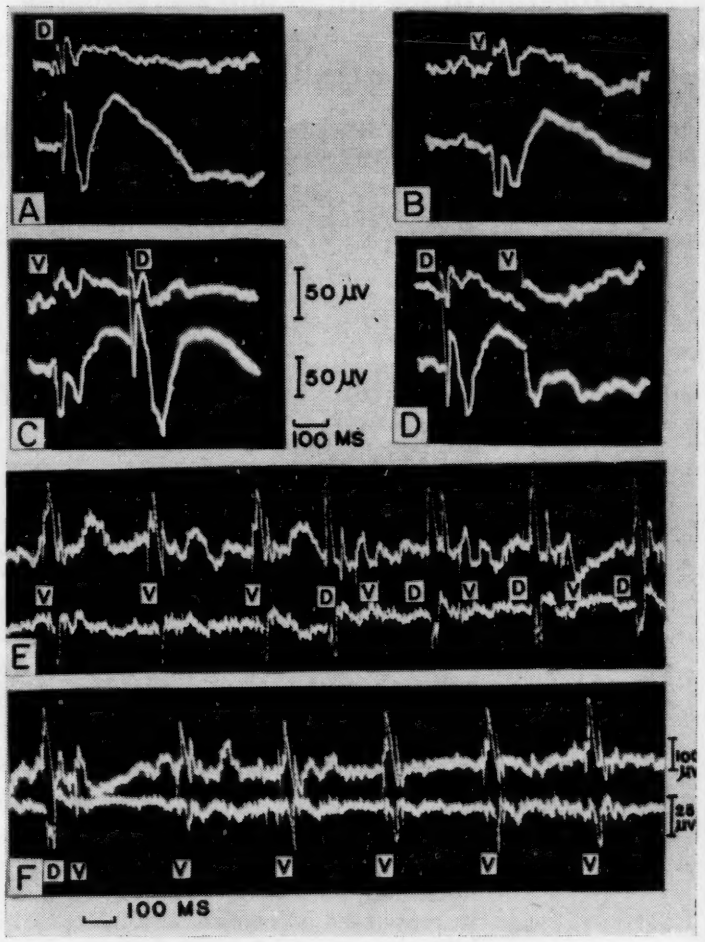


Fig. 6

Interaction patterns in the entorhinal area to hippocampal stimulation. In records A to D, upper trace is bipolar, lower trace is monopolar record. In E and F, upper trace is monopolar, lower is bipolar record. A, control response to dorsal hippocampal stimulation (7.0 V., 0.6 msec.). B, control response to ventral hippocampal stimulation (15.0 V., 0.6 msec.). C, facilitation of test response to dorsal hippocampal stimulation (D) by conditioning stimulus to ventral hippocampus (V). D, inhibition of test response to ventral hippocampal stimulation (V) by conditioning stimulus to the dorsal hippocampus (D). E, inhibition of the entorhinal test response to ventral hippocampal stimulation (V) by a conditioning dorsal hippocampal stimulus (D) 100 msec. before the test stimulus, during repetitive stimulation at 3 per sec. F, gradual recovery of the response to ventral hippocampal stimulation (V) at the end of the conditioning period. E and F are contiguous portions of the same record.

a test stimulus in the dorsal hippocampus were more complex. At 200 msec. shock spacing, facilitation of the test response in the entorhinal area was frequently seen, but at some levels in the entorhinal area no changes in the test response were seen at 200 msec. shock spacing. At 100 msec. stimulus spacing slight inhibition of the test response usually occurred. This inhibition was accentuated during repetitive stimulation at 3 per sec. with 100 msec. spacing between the paired shocks.

Thus, in summary, the results suggest significant regional differences in the patterns of connexions between the entorhinal area and different parts of the hippocampus. The evidence from interaction studies suggests that

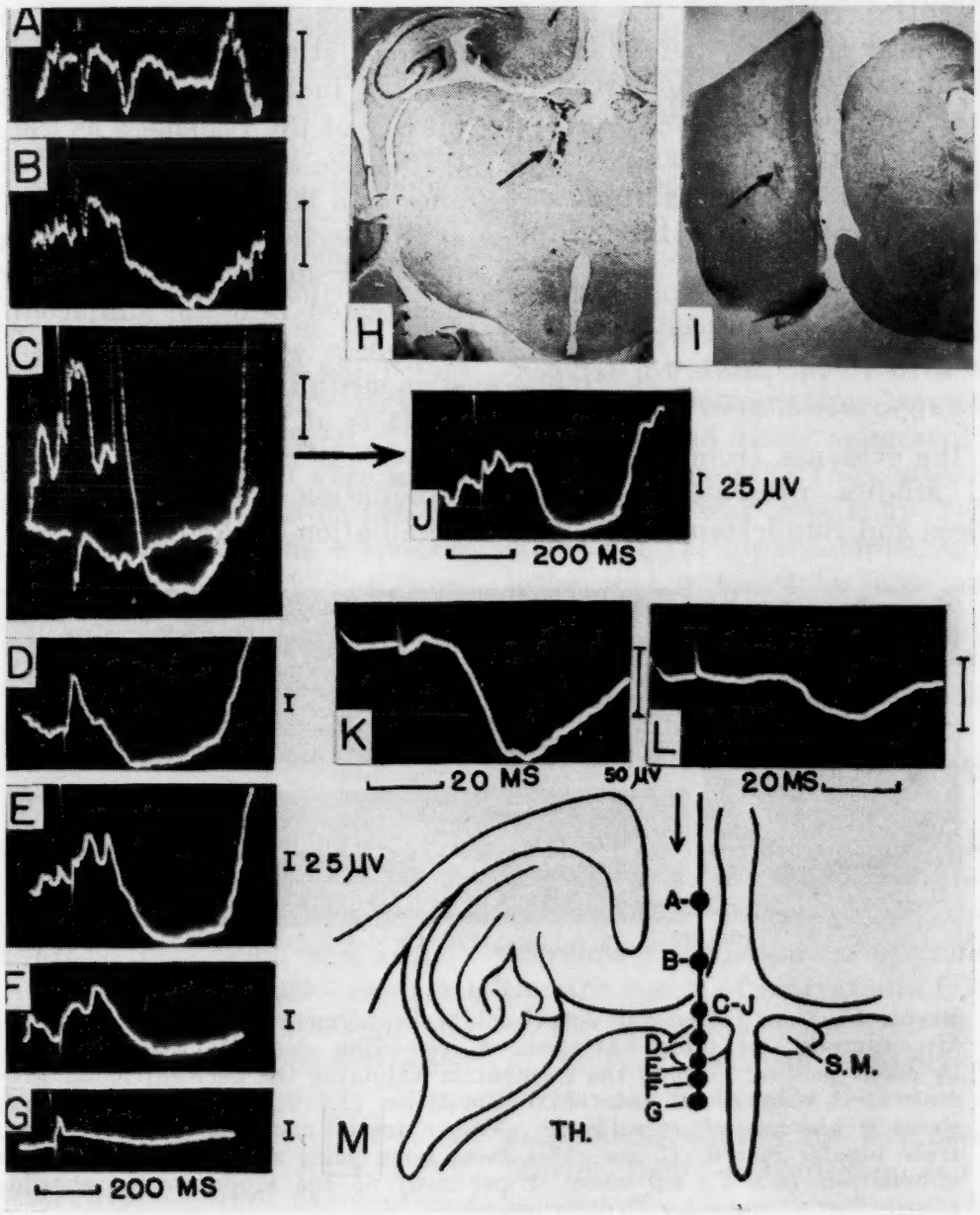


Fig. 7

Bipolar responses from cingulate cortex and stria medullaris to stimulation of the ipsilateral entorhinal area. Disposition of the recording electrode track is shown in photomicrograph H and diagram M. Tip of stimulating electrode in entorhinal area is shown in photomicrograph I. Records A to G and including J were taken at the points with the same letters in M. Record J is of the same response as C but taken at the reduced amplifier gain used in records D to G. Lower trace in C is simultaneous monopolar record. The response peaks sharply in the vicinity of the stria medullaris. Bipolar responses in the contralateral stria medullaris to stimulation of the entorhinal area (K) and hippocampus (L), with shorter latency from entorhinal stimulation. Abbreviations: S.M. stria medullaris; TH, thalamus.

an influx from the dorsal hippocampus (and thus presumably in part at least from the fornix) can exercise a controlling influence over activity in the whole length of the entorhinal area. Ventral regions of the hippocampus do not appear similarly potent in this respect. The evidence confirms, however, the presence of large connexions between ventral and dorsal regions of the hippocampus, and through these the ventral hippocampus may exert its influence on patterns of intrahippocampal integration.

4. *Efferent projections from hippocampus and entorhinal area to the midbrain tegmentum through the stria medullaris.*

In view of the evidence from experimental histological studies presented elsewhere (Adey, Merrillees and Sunderland 1956) that the entorhinal area in the marsupial phalanger projects extensively to the dorsal midbrain tegmentum through the stria medullaris, it was decided to seek physiological evidence of the extent of these connexions. The physical proximity of the overlying fornix bundles to the stria medullaris in such animals as the cat is fortunately obviated in the phalanger brain, where they are separated by 4-5 mm. (fig. 7-M). The exploring electrode was arranged to penetrate the stria medullaris vertically 2 mm. anterior to the habenular nuclei.

(*a*) *Responses recorded in the stria medullaris.*

As the recording electrode penetrated the overlying cingulate cortex, small responses were evoked by both entorhinal and hippocampal stimulation. There was a sudden marked increase in both amplitude and complexity of the responses as the electrode penetrated the stria medullaris, with the appearance of a large slow-wave following the primary deflection. There was a rapid decrement in the responses as the recording electrode penetrated into the subjacent thalamus, and responses ceased about 2 mm. deep to the stria medullaris (fig. 7 A-G).

It is of particular interest that the latencies of the responses in the stria to ipsilateral stimulation were significantly longer from stimulation of the hippocampus than from the entorhinal area, being about 5 msec. from the entorhinal area and 12-16 msec. from the hippocampus. Similar maxima in the responses to hippocampal and entorhinal stimulation were seen in the contralateral stria medullaris, with longer latencies than in the ipsilateral stria, measuring 8-10 msec. from the entorhinal area and 20-25 msec. from the hippocampus (fig. 7 K, L).

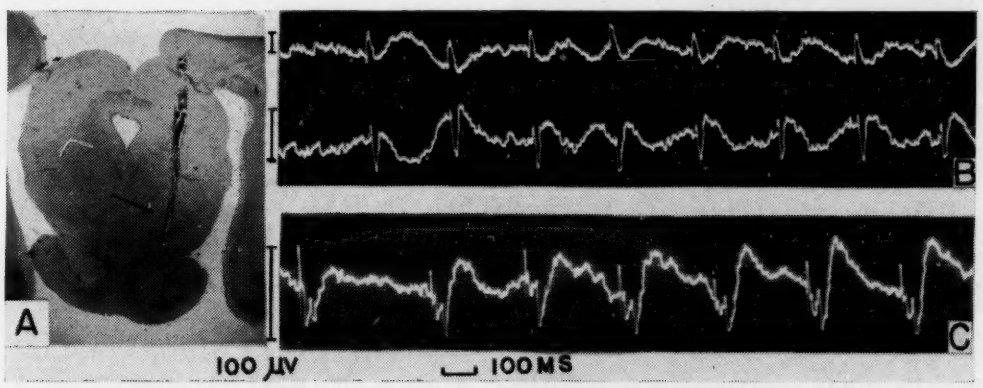


Fig. 8

Responses from ipsilateral dorsal midbrain tegmentum to stimulation of hippocampus and entorhinal area. A, recording electrode track indicated by arrow passing through the tegmentum adjoining the periventricular grey matter. B, responses to entorhinal stimulation (1.7 V., 0.5 msec., 3 per sec.) showing absence of recruitment. Upper trace, monopolar record, lower trace bipolar record. C, responses from same point as B during repetitive stimulation (4.5 V., 0.2 msec., 3 per sec.) of the hippocampus, showing recruitment of response. Bipolar record.

(*b*) *Responses recorded in the mesencephalon.*

The midbrain was explored at the intercollicular level with recording electrodes tra-

versing the tissues immediately lateral to the periventricular gray matter, since our previous histological studies had suggested that fibers from the entorhinal area terminated in this region.

Responses were recorded in the tectum and adjoining the periventricular gray matter. The ventral limit of the responsive zone appeared to lie 2 mm. ventral to the aqueduct. Here bipolar responses ceased, although small responses, presumably volume-conducted, could still be recorded in monopolar leads. Patterns of latency difference noted in the stria medullaris were preserved in the midbrain, with responses to ipsilateral entorhinal and hippocampal stimulation appearing at 5-7 msec. and 16-20 msec. respectively.

Certain interesting differences were noted between the midbrain responses to entorhinal and hippocampal stimulation. The responses to entorhinal stimulation were of shorter duration, smaller and more spike-like than those from hippocampal stimulation. Moreover, during repetitive stimulation of the entorhinal area the responses followed at rates up to 10 per sec. without evidence of recruitment or fatigue, whereas there was significant recruitment of the responses to repetitive hippocampal stimulation, suggesting a monosynaptic pathway from the entorhinal area in contrast to the projections from the hippocampus (fig 8.). A more extensive exploration of the overall extent of these rhinencephalic projections to the brainstem is in progress and will be reported elsewhere.

DISCUSSION

1. *Pattern of intrahippocampal integration.*

There are certain major difficulties in the application of the electrophysiological method to a study of this nature. It is obvious that within such an organ as the hippocampus, particularly over such short conduction distances, the evoked potentials may merely result from antidromic conduction. To preclude as far as possible fallacious interpretations in such restricted systems, evidence may be sought of transneuronal conduction to a remote site, having regard to the latency shifts which are thus necessarily involved. Orthodromic pathways involving more than one synapse may be examined for facilitation of the response under conditions of repetitive stimulation, and may be vulnerable to the phenomenon of blocking interaction (''inhibition'') when the synapses involved are subjected to afferent volleys from different sources at short intervals. These techniques have been extensively employed in this and other recent studies of rhinencephalic mechanisms, and while it may be claimed that in this way distinctions may be made between ortho- and antidromic conduction, some doubts must always remain in the absence of anatomical confirmation.

Nevertheless, the results of the present study draw attention to certain surprising differences between the observed physiological pathways and those suggested in the Papez (1937) ''circuit''. Thus although entorhinal stimulation was regularly followed by responses in the hippocampus, entorhinal stimulation was followed by only small and irregular responses in the fornix. On the other hand, stimulation of the fornix was regularly followed by responses in both hippocampus and entorhinal area. These results suggest transsynaptic conduction from fornix to entorhinal area, and thus confirm much recent work in support of the hypothesis that impulses from fornix stimulation entering the hippocampus are not merely the result of antidromic conduction in pyramidal cell axons nor the result of activation of axon collaterals of the pyramidal cells.

The evidence in support of this hypothesis may be briefly reviewed. Experimental anatomical studies by Gerebtzoff (1941-42), Morin (1950) and Sprague and Meyer (1950) suggest the presence of caudally directed fibers in the fornix. Some of these fibers may be part of a septofugal system arising in the medial septal nucleus (McLardy 1955b). Johnston (1923) noted a possible connexion from the stria medullaris to the hippocampus via the fornix. No retrograde degeneration in the hippocampal pyramidal cells has been seen after section of the fornix (Daitz and Powell 1954; McLardy 1955a).

From electrophysiological studies, Green and Arduini (1954) envisaged a pathway from the midbrain tegmentum, through the lateral hypothalamus, septum, precommissural and dorsal fornices conveying afferent activ-

ity to the hippocampus. Green and Arduini abolished the synchronous hippocampal discharge to "alerting" stimuli by lesions in the dorsal fornix or in the precommissural fornix, but not by destruction of the mammillary body. Green and Adey (1955) noted that responses evoked in the hippocampus by stimulation of the fornix had characteristics strongly suggesting that a presynaptic potential was followed by a synaptic or cellular response. They also noted that delayed wave complexes followed the primary response. Section of the alveus did not abolish the hippocampal response caudal to the section in these experiments, and examination of the "turnover" points in the response likewise suggested that afferent fibers from the fornix may run deeply within the hippocampus. It was tentatively postulated that an afferent pathway might run from the fimbria to relay on the dentate pyramids, then along the axons of the dentate pyramids to reach the pyramidal cell layer of the hippocampus. Green and Machne (1955) have observed convergence in the region of the dentate pyramids in single unit responses to a variety of peripheral sensory stimuli. After a second relay the pathway would enter the fornix once again. These experiments appeared to preclude antidromic conduction and activation of collaterals in the stratum oriens as a source of synaptic potentials. These intrahippocampal pathways may be responsible for travelling slow-waves of the type reported recently by Liberson (1955) and which may play a significant part in patterns of intrahippocampal integration.

The "turnover" in the hippocampal response to fornix stimulation seen in the vicinity of the dentate pyramids in the present study further supports the possibility of a relay in an afferent pathway in this region. Adey, Merrillees and Sunderland (1956) have noted that complete removal of the entorhinal area does not abolish the slow-wave hippocampal response to an alerting stimulus.

While it is thus possible to present a strong case in support of an afferent inflow into the hippocampus through the fornix, these results are not to be construed as excluding afferent paths from the entorhinal area in accordance with classical concepts. Indeed, the results of the present study support such an arrangement, but suggest that an inflow from the entorhinal area may be considered as capable of some modification of the general level of activity in the hippocampus, rather than as providing information which is passed directly with little modification to the fornix system.

Our results clearly suggest that there may be important regional differences in the extent of projections from the entorhinal area to the hippocampus, with bigger projections to more dorsal parts of the hippocampus than ventrally. Such dorsal projections might be capable of modifying the hippocampal responses to afferent data arriving via the fornix soon after the entry of these fibres into the deeper layers of the dorsal hippocampus. Our results have shown complex interaction patterns in this part of the hippocampus which seem intimately related to the temporal spacing between the stimuli to the fornix and entorhinal area. Since, however, a conditioning stimulus to the fornix uniformly inhibited the hippocampal test response to entorhinal stimulation, the results cannot be interpreted as indicating that the entorhinal area exercises an overriding control on the general level of hippocampal activity, although there was evidence that a conditioning entorhinal stimulus was capable of facilitating the ensuing hippocampal response to fornix stimulation.

The comparatively slow time course of the hippocampal interaction patterns raises certain problems. In our experiments it appeared that potentiation and inhibition could be elicited in appropriate circumstances at intervals of 80-300 msec. between the conditioning and test stimuli. This would imply the presence of continuing states of elevated or depressed excitability for considerable periods following single shock stimulation. Similarly prolonged potentiation lasting 200-300 msec. was seen in the cat following single stimuli to the fornix (Green and Adey 1955) and as noted by Liberson (1945) the number of pulses applied seemed more important than the duration of repetitive stimulation. Thus Green and Adey found that 9 shocks at 10 per sec. would potentiate for 2 sec. and 26 shocks at 10 per sec. for 8 sec. Prolonged bursts would sometimes potentiate for several minutes, but there was also evidence of a refractory period

following each stimulus during repetitive stimulation.

The recent careful studies of Cragg and Hamlyn (1955) have indicated very precisely that the time course of excitation in the hippocampal pyramidal cells under Nembutal anesthesia is too rapid to explain the long lasting interaction patterns which we have observed. It may be that the anesthetic agent used by Cragg and Hamlyn has specifically affected the excitability of individual pyramidal cells, or more likely, that the long duration of the interaction patterns which we have observed depend on the integrity of slow potential changes in dendritic fields which may be particularly susceptible to barbiturate anesthesia. At all events the presence of persisting changes in hippocampal excitability for 200-300 msec. after single stimuli is compatible with the regular rhythmic waves evoked in it at 2-5 per sec. during alerting or arousal by somatic, auditory or visual stimuli (Gerard, Marshall and Saul 1936; Jung and Kornmüller 1939; Maclean, Horwitz and Robinson 1952; Liberson and Cadilhac 1953; Green and Arduini 1954; Green and Adey 1955; Adey, Merrillees and Sunderland 1956). There is an obvious resemblance between these slow hippocampal rhythms and the theta rhythms seen clinically in children and emotionally disturbed adults.

2. *Hippocampal projections to the entorhinal area.*

In addition to a conduction from fornix to hippocampus, our findings suggest further projections from hippocampus to entorhinal area in the reverse direction to the circuit suggested by Papez (1937). Stimulation of the dorsal hippocampus was followed by a recruiting response even at the lower limit of the entorhinal area. It may be suggested that, although the position of the hippocampal electrode in the zone CA4 made direct excitation of alvear fibers unlikely, this recruitment was due to gradually spreading excitation within the hippocampus from activity in axon collaterals. However, no comparable recruitment could be elicited from stimulation of ventral regions of the hippocampus. This is of interest since dorsal and ventral regions of the hippocampus appeared reciprocally interconnected by major pathways. Connexions in either direction between the ventral hippocampus and entorhinal area seemed less extensive than those between dorsal hippocampus and entorhinal area.

The anatomical pathways from hippocampus to entorhinal area remain obscure, but Cajal (1911) pointed out that at least some hippocampal neurons pass to the subiculum, adjoining the entorhinal area, and that a further projection tract might arise in the subiculum running to an undetermined destination. Green and Shimamoto (1953) suggested that spread of seizure activity from the hippocampus to other cortical areas occurred through basal temporal cortex.

3. *Projections from hippocampus and entorhinal area to midbrain tegmentum running in the stria medullaris.*

Due to its configuration, the marsupial phalanger brain affords an excellent opportunity to study the role of the stria medullaris as an efferent pathway from the entorhinal area, since the stria is well removed from both hippocampus and fornix. It was found to respond to both ipsilateral and contralateral stimulation of the entorhinal area.

It is of particular interest that the responses recorded in the stria had significantly longer latencies from hippocampal than from entorhinal stimulation, and that the latency difference was of the same order (10 msec.) as the latency of entorhinal responses to hippocampal stimulation, thus supporting the concept that impulses from the hippocampus pass via the entorhinal area to the stria medullaris. Moreover, the sharp, spike-like strial responses to entorhinal stimulation were distinctly different from the longer lasting responses to hippocampal stimulation. The former conformed in many respects to the criteria of a monosynaptic pathway, while the characters of the latter suggested in their temporal dispersion and recruitment a degree of neuronal divergence between the hippocampus and entorhinal area.

Although the responses in the midbrain tegmentum to entorhinal and hippocampal stimulation were sought only at the intercollicular level, it appeared that they were essentially restricted to the dorsal region ad-

joining the periventricular gray matter. Terminal degeneration of fibers running in the stria medullaris was seen in this region following entorhinal ablation in the marsupial phalanger (Adey, Merrillees and Sunderland 1956). Stimulation of the entorhinal area produces a prolonged inhibition of upward conduction in certain central tegmental brainstem pathways which traverse the mesencephalon to the region of the centrum medianum (Adey, Segundo and Livingston 1955). Moreover, the entorhinal area exerts a more powerful influence in this respect than any other cortical area examined in the monkey. Gloor (1955 a and b) observed short latency responses from amygdaloid stimulation in the same region of the midbrain tegmentum as those in which fibers from the entorhinal area appear to terminate in our experiments. Gloor points out that these responses appear with a much shorter latency than those recorded in the immediately rostral regions of the posterior hypothalamus. Our results suggest that these short latency responses from the amygdala may also pass caudally in the contributions which the stria medullaris receives from the stria terminalis (Johnston 1923).

The findings presented here and elsewhere (Adey, Merrillees and Sunderland 1956) are thus in agreement with the concept that the hippocampus and entorhinal area may form part of a reentrant pathway, receiving caudally directed activity via the fornix from the "reticular" thalamic nuclei and the septum, and with activity passing from the entorhinal area to the midbrain tegmentum in the stria medullaris (fig. 9).

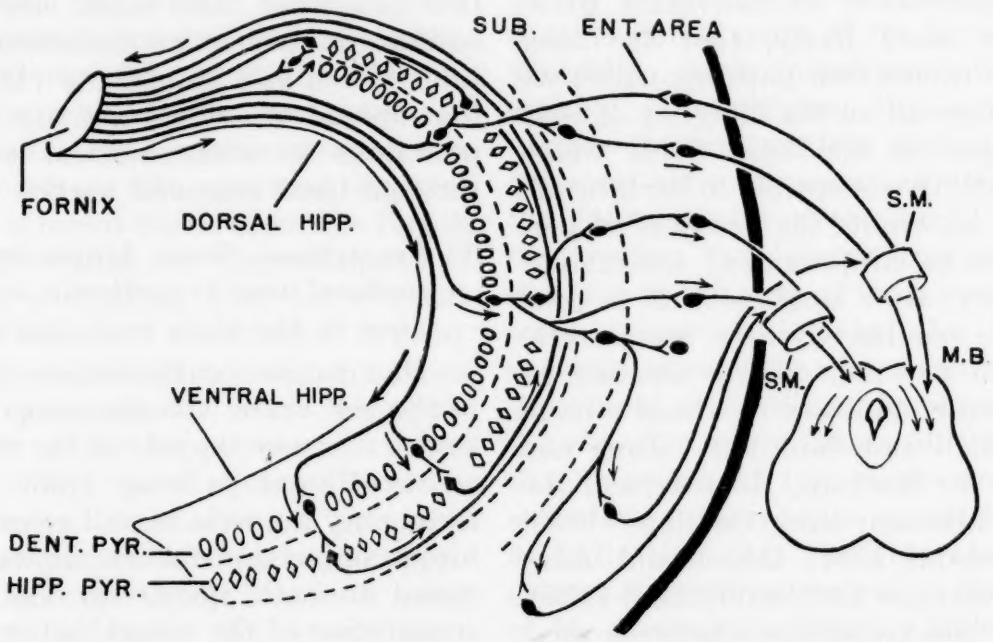


Fig. 9

A diagrammatic representation of suggested caudally directed pathways from the fornix running through the hippocampus to the entorhinal area, thence bilaterally in the stria medullaris to the midbrain tegmentum. Abbreviations: DENT. PYR., layer of dentate pyramidal cells; DORSAL HIPP., dorsal hippocampus; ENT. AREA, entorhinal area; HIPP. PYR., hippocampal pyramidal cell layer; M.B., transverse section through midbrain; S.M., stria medullaris; SUB., subiculum.

The central tegmental areas of the midbrain, the reticular thalamic, hypothalamic and septal areas of the diencephalon are themselves activated by a wide variety of sensory stimuli and form part of a "nonspecific" cortical activating system (ascending reticular system). The caudally directed activity from the entorhinal area may reenter this activating system at the midbrain level, where it may initiate further modification in the upward stream of neural activity.

SUMMARY

1. Electrophysiological investigations have been performed in the rhinencephalon of 16 specimens of the marsupial phalanger (*Trichosurus vulpecula*).

2. The reciprocity of pathways between entorhinal area, hippocampus and fornix was tested. It was found that whereas stimulation of the fornix was followed by responses in both the hippocampus and entorhinal area, stimulation of the entorhinal area evoked responses in the hippocampus, but only small irregular responses in the fornix. The findings on entorhinal stimulation thus throw some doubt on the classical concepts of Papez (1937) of major projections from entorhinal area to fornix through the hippocampal formation.

3. Interaction patterns were studied in the hippocampal responses following paired stimuli to fornix and entorhinal area. It was found that a conditioning stimulus to the fornix inhibited the test response to entorhinal stimulation. Conversely, a conditioning stimulus to the entorhinal area was followed by facilitation of the test response to fornix stimulation at many shock spacings. A "turnover" point in the hippocampal response to fornix stimulation was seen in the vicinity of the dentate pyramidal cells during progressive penetration of the hippocampal formation.

4. Interaction patterns were studied in the entorhinal area to paired shocks to widely separated points in the dorsal and ventral regions of the hippocampus. Significant differences were found in the extent of projections between these two parts of the hippocampus and the entorhinal area. Stimulation of the dorsal hippocampus was followed by large recruiting responses in the whole length of the entorhinal area. Stimulation of the ventral hippocampus was followed by entorhinal responses with much less evidence of recruitment. Stimulation of the entorhinal area was followed by smaller responses in the ventral hippocampus than in the dorsal, with fewer slow-wave trains in the ventral hippocampal responses.

5. Interaction studies suggest that an influx from the dorsal hippocampus can exercise a powerful influence over activity in the whole length of the entorhinal area. Although ventral areas of hippocampus do not appear similarly potent, the evidence suggests the presence of large projections between ventral and dorsal regions of the hippocampus through which the ventral hippocampus may exert its influence on patterns of intrahippocampal integration.

6. Efferent projections from the entorhinal area to the midbrain tegmentum have been examined. Our findings confirm previous histological studies (Adey, Merrillees and Sunderland 1956) that a bilateral efferent pathway exists through the stria medullaris from the entorhinal area. Responses in it from entorhinal stimulation have many of the characteristics of a monosynaptic pathway, and exhibit a significantly shorter latency than those induced in the stria from hippocampal stimulation. The latency differences are compatible with the concept of a hippocampal projection to the stria medullaris through the entorhinal area. Responses in the midbrain at the intercollicular level were localised to the dorsal tegmentum in a region adjoining the periventricular gray matter where our previous histological studies had suggested that fibers from the entorhinal area might terminate.

It is indeed a pleasure to acknowledge the continued enthusiastic and unfailing technical assistance of Mr. G. Edsall and Mr. I. Hine in electronic and histological matters respectively. Without their support much of this study would yet remain to be done.

REFERENCES

Adey, W. R. An experimental study of the central olfactory connexions in a marsupial. *Brain*, **1953**, *76*: 311-330.

Adey, W. R., Merrillees, N. C. R. and Sunderland, S. The entorhinal area; behavioural, evoked potential and histological studies of its interrelationships with brain stem regions. *Brain*, **1956**. In press.

Adey, W. R. and Meyer, M. Hippocampal and hypothalamic connexions of the temporal lobe in the monkey. *Brain*, **1952**, *75*: 358-384.

Adey, W. R., Segundo, J. P. and Livingston, R. B. Cortical influences on brainstem conduction. *Amer. J. Physiol.*, **1954**, *179*: 613 (abstract).

Brodmann, K. *Vergleichende Lokalisationslehre der Grosshirnrinde*. J. A. Barth, Leipzig, **1909**, 324 pp.

Cajal, S. R. *Histologie du système nerveux de l'homme et des vertébrés*. Vol. 2. A Maloine, Paris, **1911**, 993 pp.

Cragg, B. G. and Hamlyn, L. H. Action potentials of the pyramidal neurones in the hippocampus of the rabbit. *J. Physiol.*, **1955**, *129*: 608-627.

Daitz, H. M. and Powell, T. P. S. Studies of the connections of the fornix system. *J. Neurol. Neurosurg. Psychiat.*, **1954**, *17*: 75-82.

French, J. D., Amerongen, F. K. von and Magoun, H. W. An activating system in brainstem of monkey. *A.M.A. Arch. Neurol. Psychiat.*, **1952**, *68*: 577-590.

GÉRARD, R. W., MARSHALL, W. H. and SAUL, L. J. Electrical activity of the cat's brain. *Arch. Neurol. Psychiat.*, Chicago, **1936**, *36*: 675-738.

GEREBTZOFF, M. A. Notes anatomo-expérimentales sur le fornix, la corne d'Ammon et leur relation avec diverses structures encéphaliques, notamment épiphysiques. *J. Belg. Neurol. Psychiat.*, **1941-42**, *41-42*: 199-206.

GLOOR, P. Electrophysiological studies on the connections of the amygdaloid nucleus of the cat. Part I. The neuronal organization of the amygdaloid projection system. *EEG Clin. Neurophysiol.*, **1955**a, *7*: 223-242.

GLOOR, P. Electrophysiological studies on the connections of the amygdaloid nucleus in the cat. Part II. The electrophysiological properties of the amygdaloid projection system. *EEG Clin. Neurophysiol.*, **1955**b, *7*: 243-264.

GREEN, J. D. and ADEY, W. R. Afferent projections to the hippocampus of the cat and monkey. *Amer. J. Physiol.*, **1954**, *179*: 640-641.

GREEN, J. D. and ADEY, W. R. Electrophysiological studies of hippocampal connections and excitability. *EEG Clin. Neurophysiol.*, **1956**, *8*: 245-262.

GREEN, J. D. and ARDUINI, A. Hippocampal electrical activity in arousal. *J. Neurophysiol.*, **1954**, *17*: 533-557.

GREEN, J. D. and MACHNE, X. Unit activity of rabbit hippocampus. *Amer. J. Physiol.*, **1955**, *181*: 219-224.

GREEN, J. D. and SHIMAMOTO, T. Hippocampal seizures and their propagation. *A.M.A. Arch. Neurol. Psychiat.*, **1953**, *70*: 687-702.

JOHNSTON, J. B. Further contribution to the evolution of the forebrain. *J. comp. Neurol.*, **1923**, *35*: 337-481.

JUNG, R. and KORNMÜLLER, A. E. Eine Methodik der Ableitung lokalisierter Potentialschwankungen aus subcorticalen Hirngebieten. *Archiv. f. Psychiat. u. Nervenkrank.*, **1939**, *109*: 1-30.

KAADA, B. R. Somatomotor, autonomic and electrocorticographic responses to electrical stimulation of rhinencephalic and other structures in primates, cat and dog. *Acta Physiol. Scand.*, **1951**, *231*: Suppl. 83, 1-285.

LE GROS CLARK, W. E. and MEYER, M. The terminal connexions of the olfactory tract in rabbit. *Brain*, **1947**, *70*: 304-328.

LIBERSON, W. T. Time factors in elective convulsive therapy. *Yale J. Biol. Med.*, **1945**, *17*: 571-578.

LIBERSON, W. T. Emotional and psychological factors in epilepsy: physiological background. *Amer. J. Psychiat.*, **1955**, *112*: 91-106.

LIBERSON, W. T. and CADILHAC, J. C. *Proc. Amer. Psychiat. Ass.*, meeting at Los Angeles, May, **1953**.

LIBERSON, W. T. and AKERT, K. Hippocampal seizure states in guinea pig. *EEG Clin. Neurophysiol.*, **1955**, *7*: 211-222.

LORENTE DE NÓ, R. Studies on the structure of the cerebral cortex. II Continuation of the study of the ammonic system. *J. f. Psychol. u. Neurol.*, **1934**, *46*: 113-177.

MACLEAN, P. D., HORWITZ, N. H. and ROBINSON, F. Olfactory-like responses in pyriform area to non-olfactory stimulation. *Yale J. Biol. Med.*, **1952**, *25*: 159-172.

MCLARDY, T. Observations on the fornix of the monkey. I. Cell studies. *J. comp. Neurol.*, **1955**, *103*: 305-326.

MCLARDY, T. Observations on the fornix of the monkey. II. Fiber studies. *J. comp. Neurol.*, **1955**, *103*: 327-344.

MEYER, M. and ALLISON, A. C. An experimental investigation of the connexions of the olfactory tracts in the monkey. *J. Neurol. Neurosurg. Psychiat.*, **1949**, *12*: 274-286.

MORIN, F. An experimental study of hypothalamic connections in the guinea pig. *J. comp. Neurol.*, **1950**, *92*: 193-213.

PAPEZ, J. W. A proposed mechanism of emotion. *Arch. Neurol. Psychiat.*, Chicago, **1937**, *38*: 725-743.

ROSE, J. E. and WOOLSEY, C. N. Potential changes in the olfactory brain produced by electrical stimulation of the olfactory bulb. *Fed. Proc.*, **1943**, *2*: 42.

SPRAGUE, J. M. and MEYER, M. An experimental study of the fornix in the rabbit. *J. Anat.*, London, **1950**, *84*: 354-368.

Reference: ADEY, W. R., SUNDERLAND, S. and DUNLOP, C. W. The entorhinal area; electrophysiological studies of its interrelations with rhinencephalic structures and the brain stem. *EEG Clin. Neurophysiol.*, **1957**, *9*: 309-324.

PRINTED IN CANADA

CLINICAL AND LABORATORY NOTES

Editor for Western Hemisphere and Far East, R. S. SCHWAB, M.D., Boston, U.S.A.
Editor for Europe and Middle East, F. BUCHTHAL, M.D., Copenhagen, Denmark

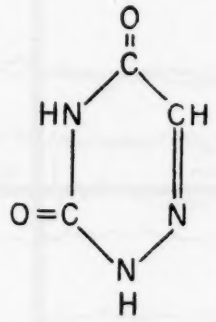
ELECTROENCEPHALOGRAPHIC AND NEUROLOGICAL CHANGES INDUCED IN MAN BY THE ADMINISTRATION OF 1,2,4-TRIAZINE-3,5 (2H,4H)-DIONE (6-AZAURACIL) [1]

C. E. Wells, M.D., C. Ajmone-Marsan, M.D., E. Frei, M.D., J. H. Tuohy, M.D. and B. I. Shnider, M.D.

National Institute of Neurological Diseases and Blindness and the National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare, Bethesda 14, Maryland

(Received for publication: December 29, 1956)

One approach to the chemotherapy of malignant diseases has been the synthesis and therapeutic trial of analogs of derivatives of the nucleotides. Among these compounds is 1,2,4-Triazine-3,5 (2H,4H)-dione, 6-Azauracil (fig. 1), an analog of uracil. This



6-AZAURACIL

Fig. 1
Formula of 6-Azauracil.

substance was first synthesized by Seibert in 1947, but he does not appear to have studied its pharmacologic properties. It has since been synthesized by a different method (Barlow and Welch 1956) and has been studied extensively by Welch and associates.

6-Azauracil is a competitive antagonist of uracil in certain bacterial strains (Handschumacher and Welsh 1956; Šorm and Škoda 1956; Škoda and Šorm 1956). Moderate antitumor activity has been demonstrated against three lymphomas (L1210, L4969, L5178) and sarcoma 180 in mice (Hakala, Law and Welch 1956) and against Ehrlich's ascites carcinoma in mice (Šorm and Šlechta 1956).

The first clinical trials with this drug were begun at Yale by Welch, Clement and Finch. In a single patient signs of central nervous system toxicity developed, associated with EEG abnormalities. Accordingly, it was felt important to attempt a study of acute and chronic toxicity of 6-Azauracil in a larger number of patients, and this program was undertaken at the National Institutes of Health.

This paper deals primarily with the effects produced by the drug upon the electroencephalogram. A parallel study on the general toxicity of 6-Azauracil is in the course of publication (Shnider, Frei and Tuohy).

MATERIAL AND METHODS

This report is based upon electroencephalographic and neurological observations made on a group of 19-patients (17 patients of the National Cancer Institute and 2 patients of the National Institute of Neurological Diseases and Blindness). These patients were given 6-Azauracil in varying dosages.

These 19 patients include 10 adults, varying in age from 16 to 64 years, and 9 children, varying in age from 3 to 12 years. Of the adults, 6 were victims of leukemia; 3, of other forms of cancer; and one, a case of severe unlocalized seizures. Of the 9 children, 8 had acute leukemia and one had a severe seizure disorder (centrencephalic) with mental and physical retardation.

The group includes 11 males and 8 females, in approximately the same ratio in both childhood and adult groups.

The 19 patients discussed were given 6-Azauracil in varying dosages and for varying periods of time, depending in part upon their general clinical condition due to the primary disease and in part upon the response to the medication. In general, the patient was begun on a relatively low dosage of the drug, i.e.,

---

1 Paper read at the Annual meeting of the Eastern Association of Electroencephalographers in New York, December 5, 1956.

from 4.5 to 9.0 mg/kg. daily in divided doses, and the drug was continued with periodic increments until toxic manifestations necessitated its discontinuance. The severity of the systemic disease sometimes limited the period during which the drug could be administered.

All patients were followed closely electroencephalographically and neurologically during the period of administration of the drug. At least one, and frequently more, baseline electroencephalogram were obtained on each patient prior to the institution of 6-Azauracil therapy. During the period of administration of the medication and immediately thereafter, frequent EEGs were obtained, at least one weekly and often as many as 4 to 5 weekly. During this time the patients were likewise followed carefully for any neurological changes.

RESULTS

Electroencephalographic changes:

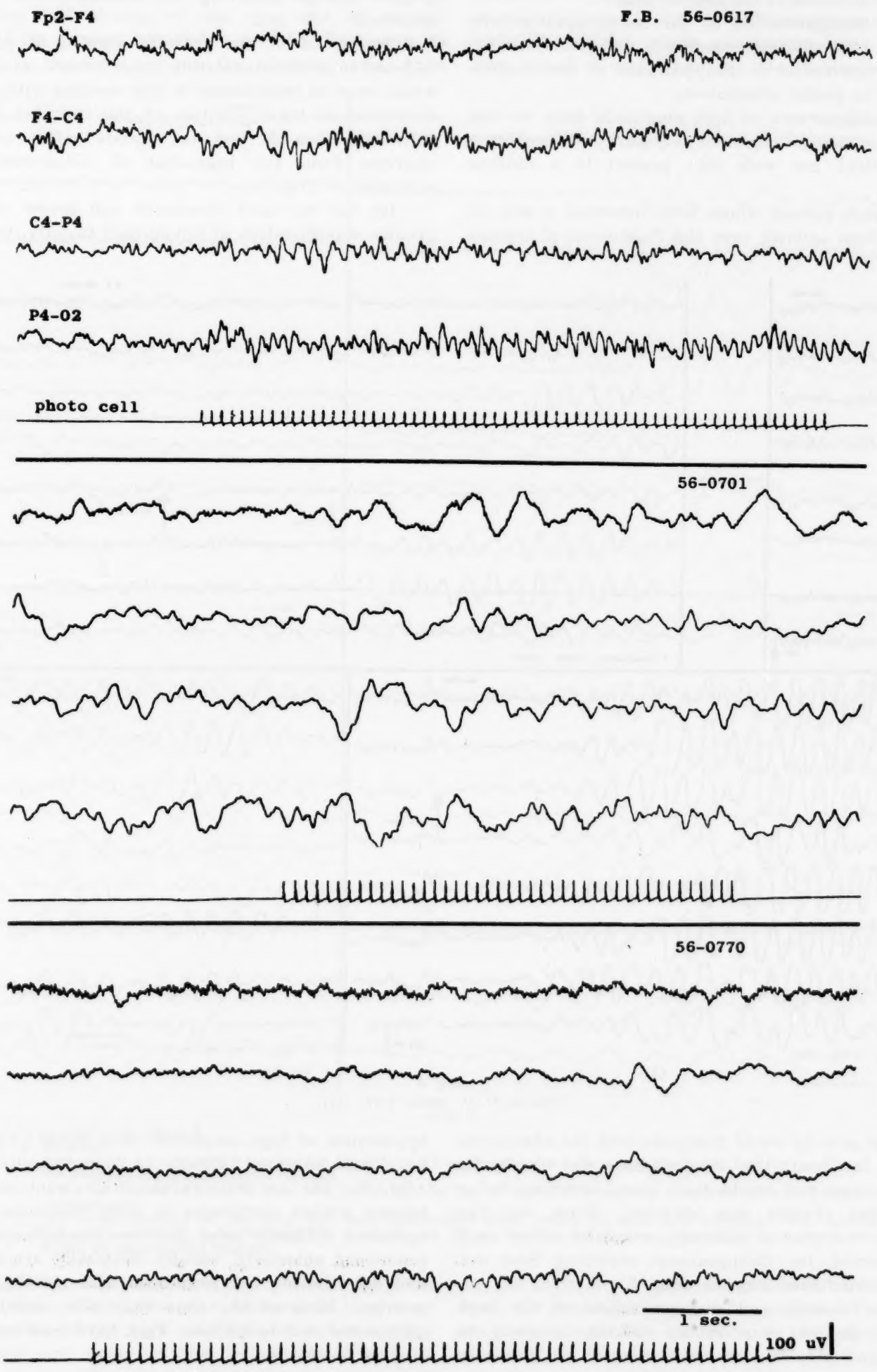
Therapy was continued to a degree sufficient to cause EEG changes in all of the patients except two (one adult who was given the medication for only 6 days; one child with mental retardation and seizures). The changes induced by 6-Azauracil may be described as follows:

Fig. 2

Serial electrographic study in one patient (C.B. male, 32 yr. old). The figures in parenthesis refer to the serial number of each record. In this and in the following illustrations, dosage of 6-Azauracil is in mg/kg/day.
In (15) the patient is disoriented in time and unable to calculate.
In (16) and (17) the patient is alert.

Fig. 3

Patient F. B. (male, 12 yr. old).
The record on top is a baseline study before administration of the drug.
The record in the middle is taken while the patient is receiving 27 mg/kg/day of 6-Azauracil.
The patient is alert.
The bottom record was taken 3 days after withdrawal of the drug.


Fp2-F4
F.B. 56-0617
F4-C4
C4-P4
P4-02
photo cell
56-0701
56-0770
1 sec.
100 uV

(*a*) abolition of the fast rhythms;
(*b*) disorganization of the background activity with moderate amplitude, irregular slowing;
(*c*) depression or disappearance of the response to photic stimulation;
(*d*) appearance of high amplitude delta rhythm.

These changes were not necessarily all present in each patient nor were they present to a uniform degree.

In each patient whose EEG exhibited a well developed beta activity over the fronto-central regions, this fast activity would disappear with the administration of the drug: this disappearance was usually the earliest sign and would take place sometime before the alpha rhythm was affected. When the fast activity was present diffusely, a similar effect could be observed, the disappearance occurring first over the anterior head regions (fig. 2).

The slowing and disorganization of the background rhythms was rather striking in every instance and this too was, as a rule, an early electrographic change following the administration of 6-Azauracil.

Almost all of the patients showing a positive response to photic stimulation under normal conditions would show an impairment in this reaction with either depression or total abolition of the occipital evoked potentials when the test was repeated after variable intervals from the beginning of 6-Azauracil administration (fig. 3).

By far the most prominent and severe electrographic manifestation of 6-Azauracil toxicity, was the appearance of high amplitude slow waves (fig. 2 to 6). These appeared initially as sporadic delta waves (fig. 5), but as the administration went on, they became almost continuous in many instances. They appeared diffusely over the two hemispheres, most prominent anteriorly, usually bilaterally synchronous and symmetrical, but sometimes with shifting asymmetries. Most of the time they were regular and rhythmical at 2 to 2.5/sec. They have been especially marked in children.

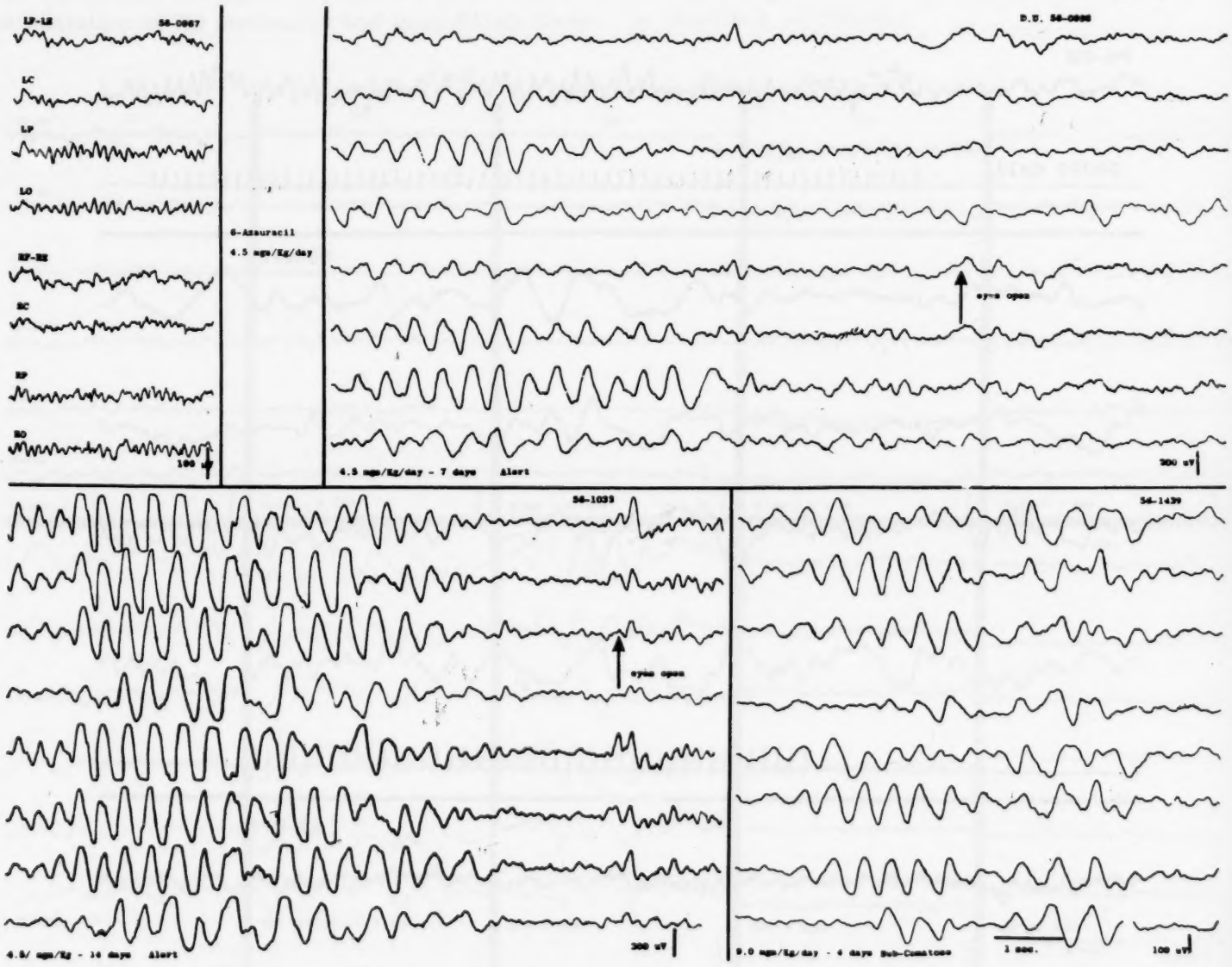


Fig. 4
Patient D. U. (male, 6 yr. old).

When this delta activity is present, the effects of opening and closing of the eyes and of arousal stimuli in general are rather variable from case to case. In the same patient, the response varies from time to time, and even during the course of the same examination. Thus, one can observe a temporary interruption of the high amplitude slow waves when the eyes are open or the patient is stimulated (acoustic or painful stimuli); at times a paradoxical reaction is present (fig. 4) with reappearance of an alpha-like rhythm which was absent when the eyes were closed. Usually, however, the various procedures do not show any obvious arousal effect (fig. 4, 5) upon the existing electrographic pattern. The hyperventilation test did not seem to be significantly sensitized by the administration of the drug.

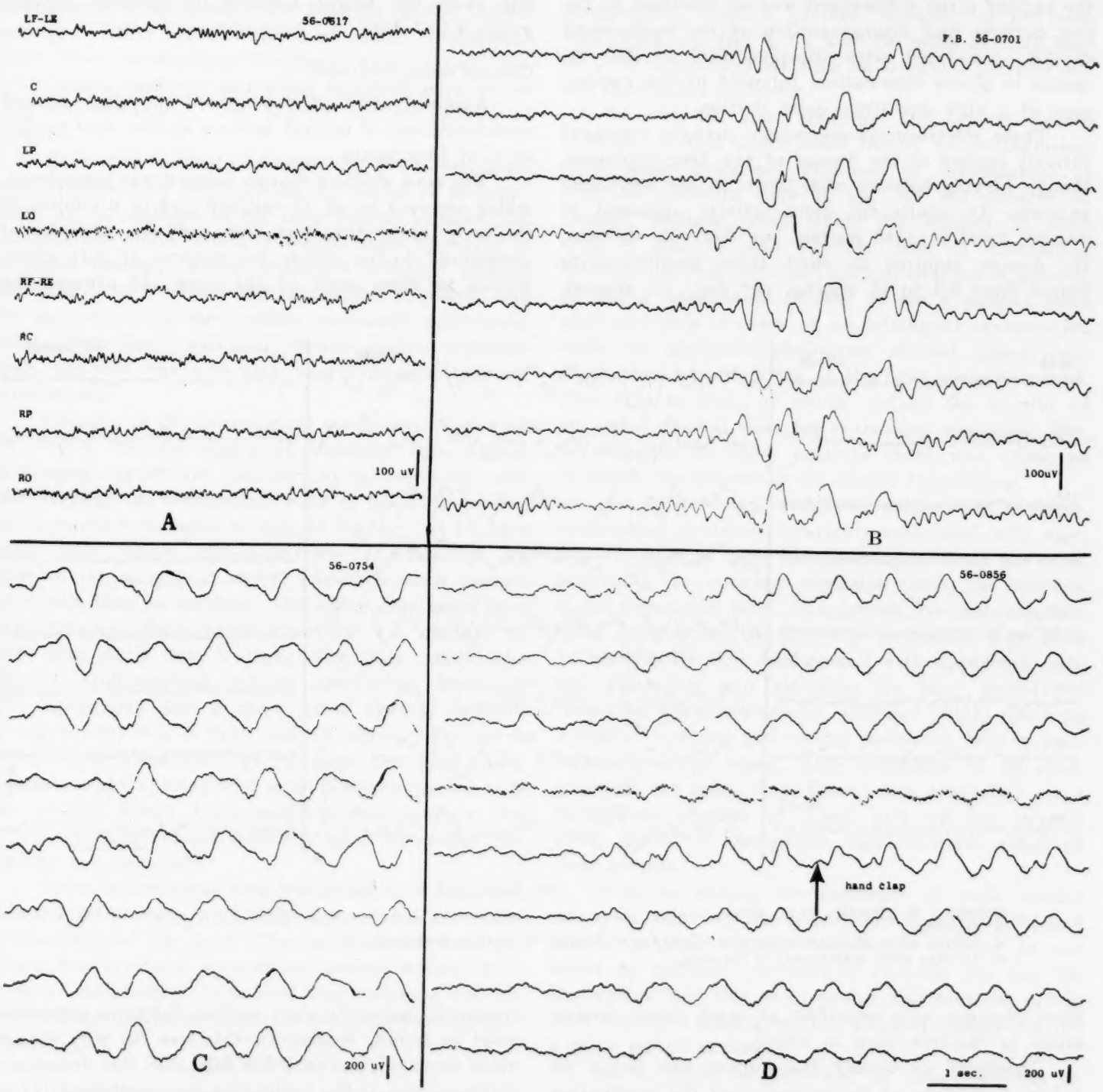


Fig. 5

Same patient of figure 3.
A. Baseline.
B. The patient has received 9 mg/kg/day for 7 days, 18 mg/kg/day for 7 days and 27 mg/kg/day for one day. No neurological or psychiatric changes.
C. After 27 mg/kg/day for 8 days and 36 mg/kg/day for 5 days. The patient is somnolent and generally unresponsive.
D. The administration of the drug has been interrupted after record C, and then resumed. The patient has since received 9 mg/kg/day for 7 days and 18 mg/kg/day for 4 days. He is quite normal and shows no neurological changes.

In 3 patients, waves tending toward sharpness were noted (fig. 2), but there were no clear-cut epileptiform discharges.

Thus the most usual electrographic response in the patient given 6-Azauracil was an abolition of the fast activity and disorganization of the background rhythm, associated with disappearance of the response to photic stimulation, followed by the appearance of a high amplitude delta rhythm.

These electroencephalographic changes appeared directly related to the dosage of the drug employed, though varying between wide limits in the individual patients. In adults the delta activity appeared at dosages from 9 to 45 mg/kg. per day. In children, the dosage required to elicit these manifestations varied from 4.5 to 27 mg/kg. per day. In general, these changes were manifest at much lower dosage levels in children than in adults.

Inasmuch as usually the subject was begun on a low daily dose of 6-Azauracil and the medication was continued with regular periodic increments until the toxic manifestations demanded its discontinuance, our information does not permit an evaluation of the chronic effects of administration of the drug at a fixed dosage level. For the few cases so studied, however, the EEG changes tend to become more severe with prolonged administration, even of the same dosage, though exceptionally temporary regression of the electrographic changes were noted, notwithstanding the fact that the patient was still under regular "treatment".

With discontinuance of the 6-Azauracil, the electroencephalogram has returned to the baseline level in each instance (fig. 2 and 6). The disappearance of the delta rhythm may be rather sudden and in any case, the record resumes its baseline pattern within 3 to 7 days.

Clinical manifestations:

Administration of 6-Azauracil provoked clinical manifestations of central nervous system dysfunction in 17 of 19 patients.

The most striking change induced was somnolence, which occurred in all 10 children and in 6 adults. In its early stage this was seen only as an unusual drowsiness during which the patient, if left alone, tended to sleep most of the time. If aroused, he appeared completely alert, and no defect in mentation could be found. Sometimes this was the only change which occurred, and in a few instances this drowsiness regressed even if the medication were continued. More usually, however, if the drug were continued, this tendency to sleep progressed and, when aroused, the patient might respond slowly and hesitantly to questions and show some difficulty in calculation and memory. If the administration of 6-Azauracil is continued for a longer period, the patient might progress to a semi-comatose state from which he could be roused to respond only with a grunt or a sigh.

This progression to a semi-comatose condition occurred in only one adult but took place in 5 children. Children showed a marked tendency to progress to

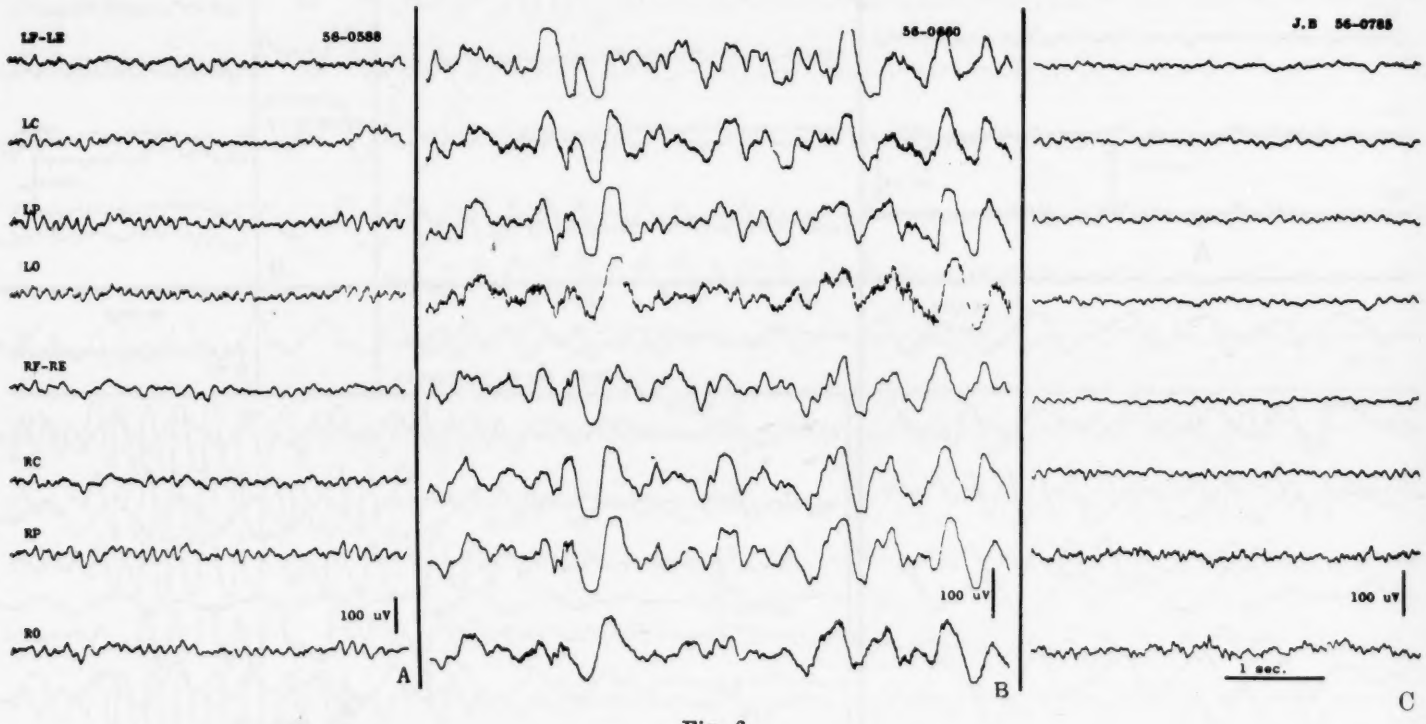


Fig. 6

Patient J. B. (female, 11 yr. old).
A. Baseline.
B. 6 days after administration of 9 mg/kg/day. Patient is alert and normal.
C. 11 days after withdrawal of the drug.

this state very quickly, so that on one day they might be only slightly drowsy while on the next, semicomatose.

While unquestionably the most marked and consistent change noted clinically was the appearance of somnolence, nevertheless a few patients showed further changes. Other manifestations of mental dysfunction seen were involuntary laughing and crying, disorientation, euphoria and acute agitation with moaning and screaming. One patient had an episode of anomia.

In a few subjects, changes in the neurological examination were noted during the course of therapy; such as, an increase in the deep tendon reflexes and unsustained ankle clonus. Babinski signs appeared in a single patient. Rarely, transient irregular jerking movements of the head and extremities appeared, and in one patient an involuntary movement reminiscent of a "liver flap" was seen. Several had an unsteady gait, but this may well have been a manifestation of drowsiness.

Changes in the neurological status have appeared at widely varying stages of therapy. One patient developed significant changes after receiving only 4.5 mg/kg. of 6-Azauracil over a 24 hour period, while another was able to take 45 mg/kg. for 12 days with only minor manifestations of toxicity. In general the margin of safety has been much greater in adults than in children. One child progressed to a semicomatose state after receiving 4.5 mg/kg. of the drug daily for 3 days. The only adult who became semicomatose did so only after receiving 27 mg/kg/day for 2 days after having received 9 mg/kg/day for 8 days and 18 mg/kg/day for 9 days. In several subjects it was noted that they might tolerate a given dosage for a considerable period with no, or only minor, toxic manifestations, only to develop severe symptoms within 1 to 3 days after the dosage was increased.

These neurological manifestations of 6-Azauracil administration have uniformly disappeared after discontinuance of the drug. The condition of most patients has returned entirely to normal within 2 to 3 days. At most, 9 days have been required for the state of mentation to reach its pre-treatment level.

DISCUSSION

Our studies have shown that 6-Azauracil provokes marked electroencephalographic and neurologic changes. The electroencephalographic modifications are usually the first and the most significant: the most severe and characteristic among these are reminiscent of those seen in other conditions, among which may be mentioned sleep, coma, certain forms of toxic and infectious encephalopathies, and certain stages of cerebral anoxia. We do not note any pattern characteristic of superficial sleep, such as spindle activity or central-vertex sharp waves, and no K complexes can be elicited with acoustic stimulation, as is the case in deeper stages of sleep. The presence of rhythmical bursts of discharges of regular slow waves at times separated by intervals in which the activity appears depressed and the record becomes flat (fig. 5) reminds one of certain tracings observed in sub-acute encephalitis. Such a pattern, however, is not constant (see i.e., fig. 4, 6) and the delta activity may be present continuously with an irregular polymorphic non-rhythmical character.

In fact, the most abnormal and typical records observed in this study could hardly be distinguished from those commonly obtained in subcomatose or comatose patients were it not for the absence of arousal changes, even when the subject is alert (fig. 4 and 5) and for the lack of correlation between electrographic and clinical changes in general. It was a remarkable finding to see a patient quite alert and able to carry on an intelligent conversation while his electroencephalogram showed almost constant delta wave activity of the type above-described. This may in part, of course, reflect the crudity of our usual clinical tests for evaluating mentation, but, nevertheless, in these patients there was often no recognizable diminution of mental functioning.

As most electroencephalographers would agree, while coma is almost invariably associated with slow, delta activity of high voltage-irrespective of the cause producing the comatose condition itself, the converse is not necessarily true. It is known, for instance, that cases of encephalitis clinically recovered, may show an abnormally slow background with apparently normal mentation and alertness for long periods of time after the acute episode. Gastaut (1954) mentions a case of a young girl having recovered from a post-traumatic coma whose EEG continued to be characterized for more than three years thereafter by a background rhythm of 3/sec. and yet her psychic state, power of abstraction and attention remained quite normal.

Notwithstanding the existence of such similar examples, however, the discrepancy between EEG and clinical picture remains remarkably striking in our series of patients, particularly because one has the impression that this is a regular and constant effect of 6-Azauracil when given in sufficient dosage and for a given period of time.

As it might be expected in those patients in whom therapy was continued in the presence of severe EEG changes, no significant electrographic deterioration could be detected when they did become semicomatose. In other cases, however, the pattern might show a further slowing of the delta rhythm. This lack of correlation was likewise seen when the drug was discontinued, the clinical signs usually disappearing several days in advance of the electroencephalogram 's returning to the baseline.

The children almost uniformly responded, both electrographically and clinically, much quicker and on smaller doses than did adults. This was most easily

demonstrated by the precipitateness with which they could change from a very slightly drowsy condition to a semi-comatose one, a state eventually reached in five children but in only one adult. EEG changes also appeared earlier and with greater severity in children than in adults. No convincing explanation for this differential response is offered, however, a possible analogy could be found in the comparably different EEG susceptibility to overbreathing of children and adults.

The mechanism and the site of action of 6-Azauracil in the production of the described central nervous system signs are as yet entirely unknown.

The similarity of its chemical structure to that of mysoline and barbital raises the possibility that all these drugs might act through a similar mechanism although the final effects, and particularly those on the EEG are quite different. The electroencephalographic picture could also suggest possible cerebral cellular anoxia. There is no evidence available to prove or disprove either of these concepts. Whatever its mode of action may be, our findings suggest that its effect is completely reversible on withdrawal of the drug.

The site of action of this drug within the central nervous system is similarly enigmatic. Some of the electrographic features prompt a consideration of the deep midline or brain stem structures as those most directly and primarily affected, but this is purely speculative, and one could equally defend the thesis of a more diffuse or even a direct cortical involvement.

This last possibility could be suggested by the rather frequently negative results of various types of stimuli upon the EEG even when the patient is clinically alert. In these cases the brain stem "arousal system" should reasonably be considered as functionally intact and the lack of appreciable electrographic arousal could be interpreted as due to a severe functional impairment of the cortical substrate upon which the impulses of subcortical (and peripheral) origin normally would exert their desynchronizing action. Studies to try to clarify its mode and site of action have been hampered by the seeming specificity of the drug's toxicity for humans. To the present, no entirely suitable experimental animal has been found manifesting the same toxic reactions as humans (cats have been given as much as 2000 mg. in a single dose intravenously without inducing any electroencephalographic change; Ajmone Marsan and Wells 1956). Thus, the number and type of experimental studies possible in the clarification of this problem have been quite limited.

SUMMARY

6-Azauracil, a new experimental anti-tumor agent, has been given to 19 patients. In 17, it has induced significant electroencephalographic and neurologic changes. EEG changes have consisted of: abolition of the fast rhythms; disorganization of the background activity with moderate amplitude, irregular slowing; depression or disappearance of the response to photic stimulation; and appearance of high amplitude delta rhythm. Clinically, the most striking change has been lethargy progressing to subcoma. The discrepancy between the electrographic changes and the clinical abnormalities has been striking, the electrographic abnormalities generally appearing considerably before those detectable clinically. All manifestations induced by the 6-Azauracil have regressed when the drug was discontinued. The changes induced were directly related to the dosage of the drug employed. Children appeared more susceptible than adults to its toxic manifestations. Its mode and site of action are unknown.

REFERENCES

AJMONE MARSAN, C. and WELLS, C. E. Unpublished observations, **1956**.

BARLOW, R. B. and WELCH, A. D. A synthesis of "6-Azauracil" (1,2,4-Triazine-3,5 (2H,4H)- dione), an analog of uracil. *J. Amer. Chem. Soc.*, **1956**, *78*: 1258-1259.

GASTAUT, H. The brain stem and cerebral electrogenesis in relation to consciousness. In *Brain Mechanisms and Consciousness,* Oxford, Blackwell Scientific Publ., **1954**, 249-283.

HAKALA, M. T., LAW, L. W. and WELCH, A. D. Inhibitory activity of 6-Azauracil, 6-uracil methyl sulfone, and related compounds on the growth of mouse lymphomas and sarcoma 180. *Proc. Amer. A. Cancer Res.*, **1956**, *2*: 113.

HANDSCHUMACHER, R. E. and WELCH, A. D. Microbial studies of 6-Azauracil an inhibitor of uracil. *Fed. Proc.*, **1956**, *15*: 267.

SEIBERT, W. Uber den Mechanismus der Reaktion von Kishner-Wolff-Staudinger, I. Mitteilung. *Chem. Ber.*, **1947**, *80*: 494-502.

ŠKODA, J. and ŠORM, F. Antagonismus 6-Azauracilu a nekterych pyrimidinovych derivatu v *Escherichia coli. Chem. listy*, **1956**, *50*: 1165-1168.

ŠORM, F. and ŠKODA, J. 6-Azauracil, antimetabolit uracilu a cytosinu v *Escherichia coli. Chem. listy*, **1956**, *50*: 827.

ŠORM, F. and ŠKODA, J. 6-Azauracil, an antimetabolite of uracil and cytosine. *Coll. Czech. Chem. Comm.*, **1956**, *21*: 487-488.

ŠORM, F., JAKUBOVIČ, A., ŠLECHTA, L. The anticancerous action of 6-Azauracil (3,5-dioxo-2,3,5-tetrahydro-1,2,4-triazine). *Experientia*, **1956**, *12*: 271.

Reference: WELLS, C. E., AJMONE-MARSAN, C., FREI, E., TUOHY, J. H. and SHNIDER, B. I. Electroencephalographic and neurological changes induced in man by the administration of 1,2,4-Triazine-3,5 (2H,4H)-dione (6-Azauracil). *EEG Clin. Neurophysiol.*, **1957**, *9*: 325-332.

PRINTED IN CANADA

ELECTROENCEPHALOGRAPHIC CHANGES INDUCED BY THE INTRAVENOUS ADMINISTRATION OF ACETAZOLAMIDE [1] (DIAMOX) IN EPILEPTIC PATIENTS

C. Saldías, M.D., F. Cabieses, M.D. and E. Eidelberg, M.D.

Department of Neurosurgery, Instituto Nacional de Enfermedades Neoplásicas, Lima, Perú

(Received for publication: September 26, 1956)

The reports of Bergstrom (1952), Lombroso *et al.* (1956), Merlis (1954) and other authors have clearly shown the value of acetazolamide (Diamox) as an efficient anticonvulsant in some epileptic patients. The mechanism of action of the drug, however, has not yet been sufficiently elucidated, although the clinical and some experimental observations permit some insight into it.

At first it was believed that the acidifying and dehydrating effects of this non-mercurial diuretic, apparently resembling those of the ketogenic diet, might account for its anticonvulsant action. However, the work of Leaf, Schwartz and Relman (1954) and the observations of Lombroso, Davidson and Grossi-Bianchi (1956) in patients under constant treatment with the drug, have clearly shown that the acidosis and dehydration obtained are short-lived, and the diuretic effect of acetazolamide is rather poor in non-edematous patients. Moreover, Davenport and his group (1946) have found that the experimental convulsive seizures produced by electric-shock are not influenced in one way or the other by rather extreme changes in the blood pH.

With these facts in mind, and taking into account that the best clinical results have been obtained in those patients who showed the most marked alterations of their EEG with the hyperventilation test (Lombroso *et al.* 1956; Merlis 1954), we studied the immediate effects of intravenous acetazolamide on the EEG recordings of a small group of epileptic patients.

MATERIAL AND METHODS

The subjects were 16 patients, male and female, of ages ranging from 10 to 55 years, with varied manifestations of epilepsy, the majority of which had not been adequately controlled by the usual anticonvulsant drugs, including hidantoines, barbiturates, oxazolidines and primidone in high dosage. They were classified on the basis of their EEG abnormality at rest without activation of any kind in the following groups:

Group 1. Slow diffuse abnormality
- (*a*) Straight: cases 1, 6, 8, 14, 16
- (*b*) With paroxysmal slow waves and spikes: cases 2, 4, 15
- (*c*) With diffuse spiking activity: cases 12, 13, 7
- (*d*) With a single spiking focus: case 5.

Group 2. Active spike or slow wave focus on an otherwise normal record: cases 3 and 10.

Group 3. Three-per-second ''wave-spike'' abnormality (petit-mal): case 9.

Group 4. Diffuse slow abnormality in one hemisphere, with a focus of spikes and slow waves: case 11.

The recording was performed with an Offner six-channel electroencephalograph, model D. Only ''monopolar'' leads were used, with both ears interconnected as the reference electrode. The electrodes were set in the standard positions according to Gibbs and Gibbs. The anticonvulsant drugs in use were not suspended.

Preliminary standard overbreathing test was done on all patients by having them inhale and exhale deeply for 3 min. at a rate of 20 to 25 complete respirations per min.

The hyperventilation test gave a ''positive'' response, with paroxysmal discharges of high-voltage slow waves, with or without spikes, which persisted for more than 30 sec. in the majority of cases, with the exception of cases 10, 11, 12 and 13 in whom only moderate increase of the basic frequency or some random slow waves were obtained.

About 10 min. after completion of the hyperventilation test, acetazolamide was injected intravenously in a dosage of 10 mg. per kilo of body weight, dissolved in 10 cc. of distilled water. The injection was completed in 15-30 sec. A continuous EEG record was obtained during the following 30 min. Except in case 5 who did not cooperate well the hyperventilation test was repeated 15 and 30 min. after the injection.

In no case were discomfort or toxic reactions observed as a result of the injection.

1 The acetazolamide used in this study was obtained through the courtesy of Lederle Laboratories Division, American Cyanamid Co., Pearl River, N.Y.

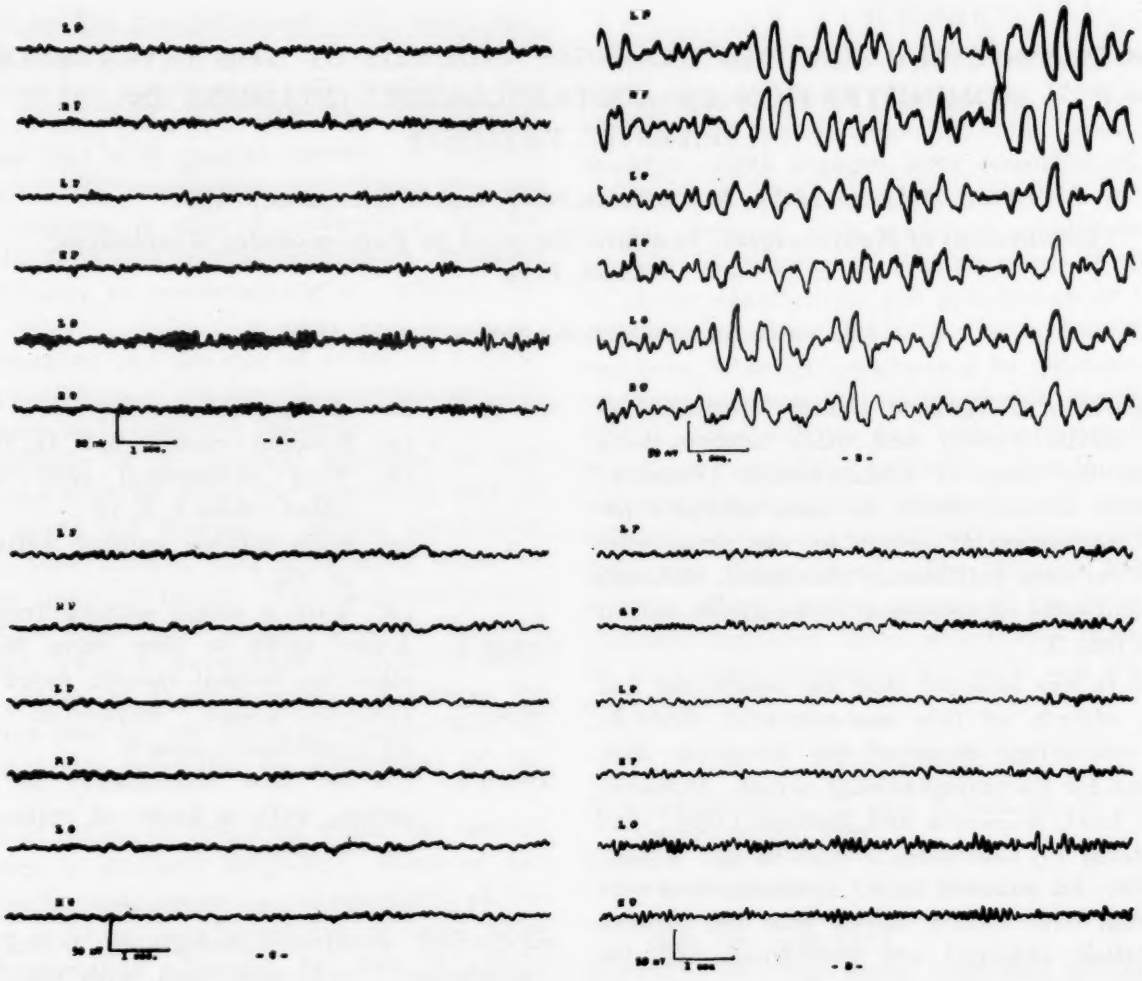


Fig. 1

A. Recording at rest.
B. After 3 min. of hyperventilation.
C. Five min. after intravenous injection of Diamox (10 mg. per kg. body weight).
D. Hyperventilation after administration of Diamox.

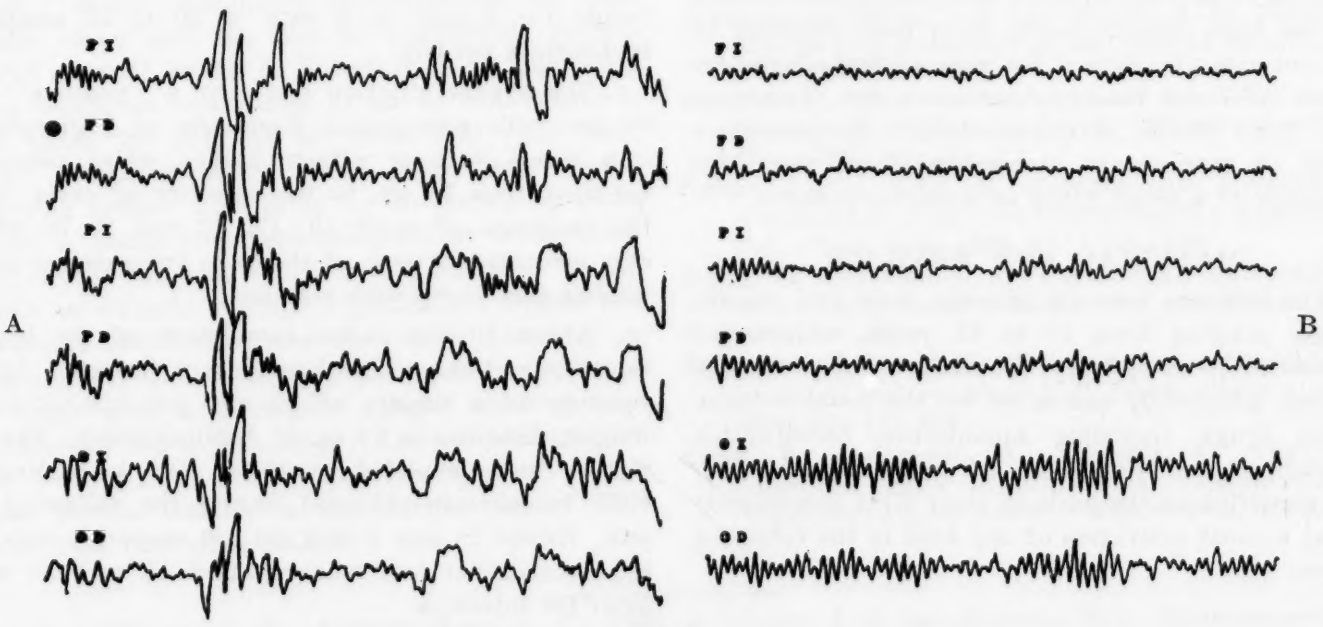


Fig. 2

A. Recording at rest.
B. Five min. after intravenous injection of Diamox (10 mg. per kilo body weight).

RESULTS

The results are classified as follows:

1. Without modification of the abnormalities of the basal record:
   - (*a*) without modification of the hyperventilatory response: cases 10, 11, 12 and 13;
   - (*b*) with marked reduction or suppression of the hyperventilatory response: cases 3, 6, 7, 8, 9 and 16.

2. With evident reduction of the basal record abnormalities:
   - (*a*) without modification of the hyperventilatory response: cases 1, 2 and 4;
   - (*b*) with marked reduction or suppression of the hyperventilatory response: cases 14 and 15.

In brief, we can say that the drug produced evident changes in the abnormalities of the EEG in 3 cases, and produced a marked reduction or total suppression of the abnormal discharges after hyperpnoea in 8 cases.

It is significant that in those cases (10, 11, 12, 13) in which there was very little or no variation on hyperpnoea before the drug was given, there was practically no modification of the record after injection of the drug.

The photographs show typical tracings although it is true that epileptic electrical activity tends to be paroxysmal and it is possible to find some periods of normal or almost normal record between seizure bursts, which might be interpreted as variations caused by the drug in study, it must be taken into account that no subject was selected for this experiment who did not show permanent abnormalities in the previous and the present recordings.

Since the experiments were performed, many of these patients have been receiving treatment with acetazolamide by the oral route. The results will be reported separately, but it may be stated that they closely resemble the effects shown by the intravenous test.

DISCUSSION

As stated above, there remains little doubt of the value of acetazolamide (Diamox) as an useful anticonvulsant. This has been clearly shown in the clinical trials of Lombroso *et al.* (1956) Muñóz and Gomensoro (1955) and Merlis (1954). Those authors found that the best results were obtained in cases with severely abnormal electrical response to voluntarily induced hyperpnoea. From such clinical findings it was postulated (Merlis 1954) that the mechanism of action was at the level of the nerve fibers, by the inhibition of carbonic anhydrase, which would give rise to an elevation of the CO_2 concentration. As Lorente de Nó (1948) has shown experimentally, the increase in CO_2 content around a nerve axon causes a total or partial blocking of the nervous impulse, an effect that is independent of the pH of the medium. There are, however, some serious objections to this hypothesis. In the first place, the distribution of carbonic anhydrase in the brains of different species of mammals does not correspond exactly to that of the white matter (Ashby 1944a, b, c, 1948; Ashby *et al.* 1952). Moreover the absence of carbonic anhydrase in the spinal cord of the pig (Ashby 1944c) suggests that this enzyme is not absolutely necessary for the transmission of the nervous impulse; its inhibition, therefore, could hardly be expected to produce a block such as that obtained by Lorente de Nó in other experimental conditions.

On the other hand, the work of Tschirgi (1954) and his group seems to indicate that carbonic anhydrase has an important function in the water and electrolyte exchange across the neuronal membrane. This assumption correlates well with the results obtained by Millichap *et al.* (1955), who inhibited the tonic phase of electrically induced seizures in mice with acetazolamide, a fact which is better accounted for by a mechanism acting at the neuronal level.

Since, as shown by our experiments, the effects of acetazolamide on certain EEG abnormalities are obtained almost immediately after intravenous injection of the drug, it is probable that its action is not to any degree due to dehydration and acidosis, which are usually slower processes. The fact that Diamox decreases the bio-electric response to hyperventilation may be due to a direct action on the central nervous system or to a modification of the effect of hyperventilation on the CO_2 content of the circulating blood, since carbonic anhydrase regulates the elimination of CO_2 by the lung. It is proposed, therefore, to repeat our experiments in the future with simultaneous determination of CO_2 in the blood and expired air.

SUMMARY

Intravenously administered acetazolamide (Diamox) abolishes or decreases certain EEG abnormalities observed in epileptic patients and blocks the paroxysmal slow-wave discharges provoked by hyperventilation in some cases. The theoretical implications of these results are discussed.

REFERENCES

ASHBY, W. A parallelism between the quantitative incidence of carbonic anhydrase and functional levels of the CNS. *J. Biol. Chem.*, **1944**a, *152*: 235-240.

ASHBY, W. On the quantitative incidence of carbonic anhydrase in the CNS. *J. Biol. Chem.*, **1944**b, *155*: 671-679.

ASHBY, W. The pattern of distribution of carbonic anhydrase in the lower cerebrum of man compared with that of certain of the lower animals. *J. Biol. Chem.*, **1944**c, *156*: 323-329.

ASHBY, W. Carbonic anhydrase in the pallium of primates compared with that of the lower animals. *Proc. Soc. Exper. Biol. Med.*, **1948**, *67*: 17-18.

ASHBY, W., GARZOLI, R. F. and SCHUSTER, E. M. Relative distribution patterns of three brain enzymes, carbonic anhydrase, choline esterase and acetyl phosphatase. *Amer. J. Physiol.*, **1952**, *170*: 116.

BERGSTROM, W. H., GARZOLI, R. F., LOMBROSO, C., DAVIDSON, D. T. and WALLACE, W. M. Observations on the metabolic and clinical effects of carbonic anhydrase inhibitors. *Amer. J. Dis. Child.*, **1952**, *84*: 771-772.

COHEN, M. E. and COBB, S. Anticonvulsive action of azosulfamide in patients with epilepsy. *Arch. Neurol. Psychiat.*, Chicago, **1941**, *46*: 676-694.

DAVENPORT, H. W. Carbonic anhydrase in tissues other than blood. *Physiol. Rev.*, **1946**, *26*: 560-573.

HENDLEY, C. D., DAVENPORT, H. W. and TOMAN, J. E. P. Effect of acid-base changes on experimental convulsive seizures. *Amer. J. Physiol.*, **1948**, *153*: 580-585.

LEAF, A., SCHWARTZ, W. B. and RELMAN, A. S. Oral administration of a potent carbonic anhydrase inhibitor (Diamox): changes in electrolyte and acid-base balance. *New England J. Med.*, **1954**, *250*: 759-764.

LOMBROSO, C. T., DAVIDSON, D. T. and GROSSI-BIANCHI, M. L. Further evaluation of acetazolamide (Diamox) in the treatment of epilepsy. *J. A. M. A.*, **1956**, *160*: 268-272.

LORENTE DE NÓ, R. Studies in nerve function. *Studies from the Rockefeller Inst. for Med. Res.*, **1948**, 131.

MILLICHAP, J. G., THATCHER, L. D. and WILLIAMS, P. M. Anticonvulsive action of acetazolamide, alone and associated to ammonium chloride. *Fed. Proc.*, **1955**, *14*: 370.

MERLIS, S. Diamox, a carbonic anhydrase inhibitor. Its use in epilepsy. *Neurology*, **1954**, *4*: 863-868.

MUÑOZ, J. G. and GOMENSORO, J. B. Personal communication, **1955.**

SALDIAS, C. A., EIDELBERG, E. and CABIESES, F. Report to the Peruvian Neuropsychiatric Society, September **1955.**

TSCHIRGI, R. D., FROST, R. W. and TAYLOR, J. L. Inhibition of CSF formation by a carbonic anhydrase inhibitor (Diamox). *Proc. Soc. Exper. Biol. Med.*, **1954**, *87*: 373-376.

Reference: SALDÍAS, D., CABIESES, F. and EIDELBERG, E. Electroencephalographic changes induced by the intravenous administration of acetazolamide (Diamox) in epileptic patients. *EEG Clin. Neurophysiol.*, **1957**, *9*: 333-336.

PRINTED IN CANADA

ELECTROENCEPHALOGRAPHIC ARTIFACT ARISING FROM DENTAL RESTORATIONS [1]

RHODA FEINSTEIN MILNARICH, B.A.,[2] GARFIELD TOURNEY, M.D. and PETER G. S. BECKETT, M.B.
Psychophysiological Laboratories, Lafayette Clinic, Detroit 7, Michigan

(Received for publication: October 22, 1956)

INTRODUCTION

Artifact closely resembling the electrical activity of the brain is often difficult to evaluate. The ringing of the telephone can cause a burst of high voltage 20 c/sec. waves. Eye movement can simulate a focus or paroxysmal activity. Movement of the patient or objects close to the patient can do the same. In fact, the life of the electroencephalographer contains so many pitfalls with regard to artifact that many electroencephalographers consider all unusual waves as artifact until proved otherwise.

Artifact resulting from dental restorations of dissimilar metals was noted on a 44-year-old male patient with a number of somatic complaints, especially referable to his head. There were no abnormal neurological findings. The electroencephalogram was essentially within normal limits with the exception of a diffuse, spike-like discharge and sharp waves which were most prominent anteriorly and temporally. Although several of the discharges resembled sharp wave activity, the technician was suspicious because some discharges were artifactual in appearance. All discharges appeared under the frontal and anterior temporal electrodes and it was known that the patient had both gold and aluminum restorations in his mouth.

Electrodes were placed on the patient's face close to his lips — one over the area of the gold inlay and the other over the aluminum restoration. One channel of the electroencephalograph was devoted to this linkage. Innumerable discharges were recorded; some of these synchronized with the spike-like and sharp wave discharges recorded from the anterior temporal electrodes (fig. 1).

To confirm the finding that the discharges were actually the result of the dissimilar metals in the patient's mouth, 45 subjects with no known neurological or psychiatric disorder were tested.

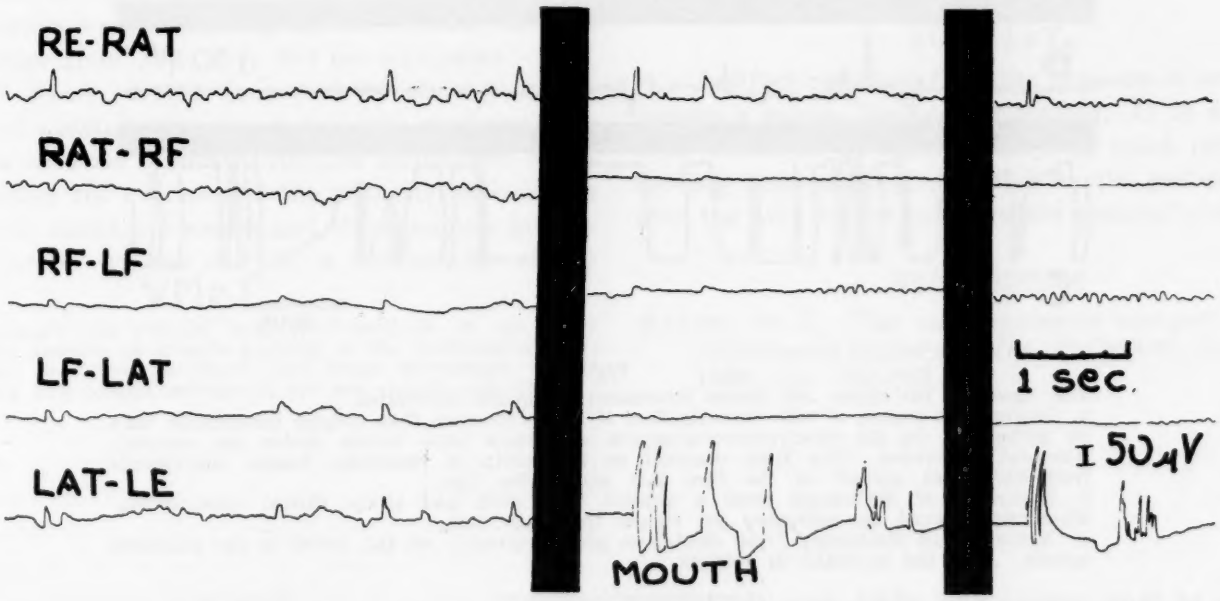


Fig. 1
Synchronization of discharges from metal restorations in mouth with discharges from anterior temporal electrodes. In the last two strips, the fifth channel is recorded from electrodes placed on the subject's face over the area of the metals.

SUBJECTS AND METHODS

The subjects fell into three groups: group I (12 subjects) had two metals in the mouth; group II (30 subjects) had only one type of metal in the mouth; group III (3 subjects) had no metal in the mouth. The pH of the saliva was determined for

1 Read at meeting of The Eastern Association of Electroencephalographers, Hartford, Conn., September 30, 1956.
2 Present address: 8305 Saturn Place, El Paso, Texas.

each subject.[1] Currents were measured with a microammeter and ranged from one-half to 40 microamperes.

For all subjects, frontal and anterior temporal electrodes were applied and electrodes were also placed on the face just above the lips. In group I, one electrode was placed over the gold area and the other over the silver area. For group II, the current was measured and the electrodes were placed over the area of those restorations which gave the highest reading in microamperes. In group III, the electrodes were placed at the upper right and lower left corners of the mouth. Recordings from these electrodes were then made. Each subject was asked to move his tongue about, swallow, bite, and speak during the recording.

RESULTS

None of the 30 subjects with only one type of metal in the mouth showed an electrical discharge accompanying mouth movement. None of the three subjects without metal showed these discharges. Of the 12 group I subjects, 7 showed discharges from the electrodes placed about the lips. For 4 of these subjects, the discharge was reflected in the electroencephalogram (table I).

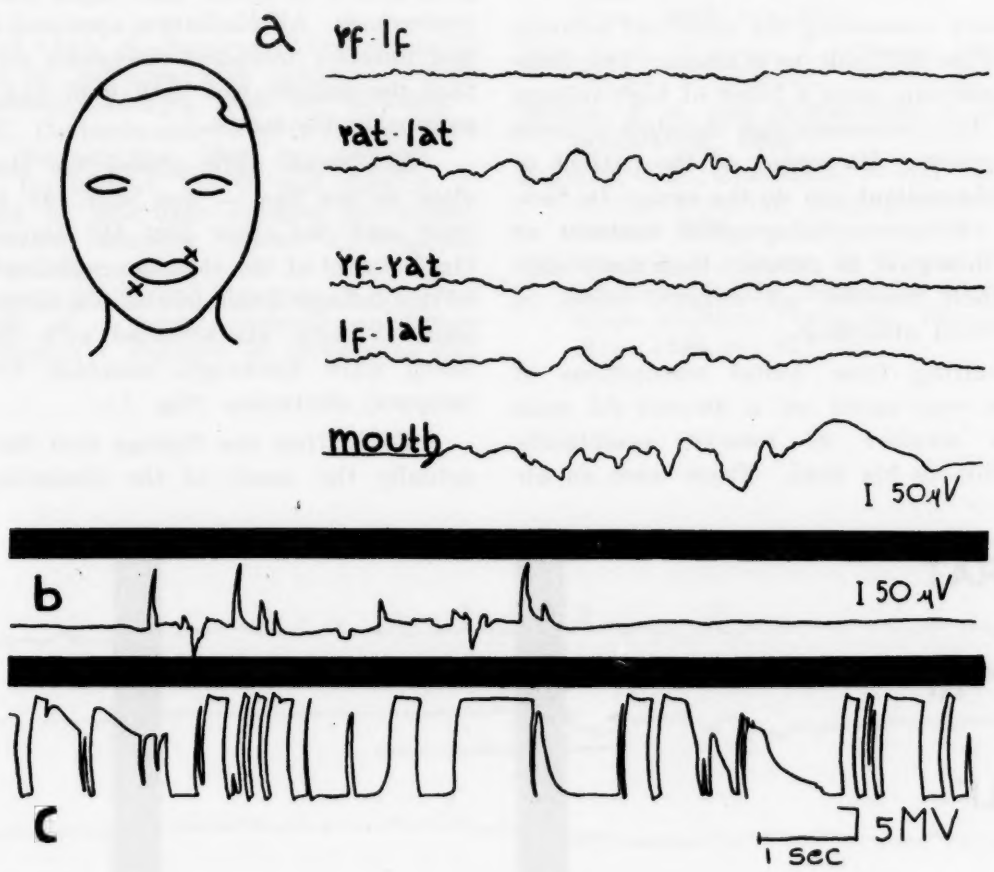


Fig. 2
The figure in the upper left shows placement of mouth electrodes.
a. During the course of this investigation it was also seen that tongue movements may be picked up on the electroencephalogram and show slow waves under the anterior temporal electrodes. The fifth channel in this strip is recording tongue movements from electrodes placed on the face just above the lips.
b. Recording of discharges from a subject with gold and silver dental restorations. Electrodes placed as indicated on figure in upper left.
c. Recording of discharges from electrodes placed directly on the metal in the subject's mouth. Note the increase in voltage.

TABLE I

Tabulation of results obtained when recording was made from electrodes placed on the face in the area of the metals.

	Total No. of subjects	Spikes recorded from lip area	Synchronous spikes seen in EEG
Group I	12	7	4
Group II	30	0	0
Group III	3	0	0

Further to test the hypothesis that these discharges came from the metal in the subject's mouth,

[1] The pH of the mouth is important from the dental point of view because an acid condition supplies more metallic salts to form a component of the battery and hence contributes to an increase of the current. However, there was no significant relationship between the pH and whether or not discharges were recorded in the present series. The mean pH of all subjects with spikes was 6.0 and the mean pH of all subjects who did not show spikes was 6.1. A t test of the difference between these means was clearly not significant.

electrodes were applied directly to the restorations of 5 group I and 7 group II subjects who had a bite sufficiently good to hold the electrode in place.[1]

The 5 subjects with dissimilar metals (group I) in their mouth showed discharges when recording directly from the restorations. Of the 7 subjects (group II) with just one type of metal in the mouth, 5 showed discharges when recording directly from the dental restoration (fig. 2).

In all cases, the characteristic high voltage discharges appeared only when the subject moved his tongue, swallowed or spoke.

DISCUSSION

Ordinarily, dental restorations are not associated with artifact on the electroencephalogram. The most common artifact seen in patients with dentures appears as muscle artifact and is usually eliminated by asking the patient to remove the dentures. However, artifact may arise when a patient has restorations of dissimilar metals.

The dental profession has long recognized the existence of a great diversity of current intensities in a mouth containing orthodontic appliances and dental restorations of dissimilar metals (Hyams 1933). The two metals set up a battery in the conducting medium of the saliva and, depending on the metals, the currents range from .5 to over 100 microamperes.

The direct current generated by these batteries would not normally be recorded on the electroencephalograph with its condenser-coupled amplifiers. However, neither the current nor the potential is constant because of mouth movement and the changing quality of the saliva. If the current is sufficiently strong and the voltage sufficiently high, the changing potentials may be recorded on the electroencephalograph.

Although all subjects with metal in the mouth have a demonstrable current, not all show this artifact on the electroencephalogram. The direction of the current flow in relation to electrode placement on the head may be partially responsible. Another factor may be insufficient voltage.

However, when several large metallic restorations are present, it is possible that the currents will interfere with the electroencephalogram. Especially if dissimilar metals far apart in the electrochemical series are used, the discharges may closely resemble spike or sharp wave activity when picked up. Even when the wave form is frankly artifactual, knowledge of the possible effect of metallic restorations may save needless checking of equipment and changing of electrodes.

It is therefore suggested that when patients show spike or sharp wave charges of unknown origin, particularly from frontal areas, and it is known that the patient has restorations of dissimilar metals, recording from the face over the area of the dissimilar metals may help to determine whether the discharges originate in the patient's brain or in his mouth.

SUMMARY

Artifact resulting from the presence of metal in a patient's mouth has been described. It is suggested that this type of artifact may be ruled out by recording from electrodes placed on the patient's face over the area of the metal in the patient's mouth.

REFERENCES

HYAMS, B. L. The electrogalvanic compatibility of orthodontic materials. *Int. J. Orthod. Dent. Chil.* **1933**, *19*: 883-888.

1 Although the subject held the electrode in place by biting, the absence of muscle activity in the electroencephalogram may be taken as proof that these discharges during swallowing and tongue movement are not muscle activity.

Reference: MILNARICH, R. F., TOURNEY, G. and BECKETT, P. G. S. Electroencephalographic artifact arising from dental restorations. *EEG Clin. Neurophysiol.*, **1957**, *9*: 337-339.

PRINTED IN CANADA

suitable amplification (V4) are available at low impedance from a cathode follower (V5). During the intervals between gating pulses, the relative potentials at the cathodes of V5 and V6 are such that points A1 and A2 (fig. 2) are effectively tied to the cathodes of V6A and V6B, via the conducting diodes V7A and V7B, respectively. The fluctuating voltages at the cathode of V5A and V5B accordingly appear almost entirely across the 22K series resistors, R1 and R2, respectively. At the same time, the potentials at the electrodes of V8A and V8B are such that the tube is nonconducting: the cathode of V8B, being connected to the relatively high potential at the cathode of V7B, is at a higher potential than the plate of V8B; and the plate of V8A, being connected to the effect of V6 (via V7) thus removed, the potentials at A1 and A2 (fig. 2) become the same; V8 now acts as a shunt, connecting the cathode of V5 (via the 22K resistors) to the storage condensers C1 and C2: V8A conducts for negative changes of the potential at the cathode of V5, and V8B conducts for positive changes of this potential.

At the end of the gating pulse, the previous conditions are resumed, and the storage circuit retains the instantaneous voltage at the cathode of V5 at the end of the last gating pulse until the incidence of the next one. At this time, the new instantaneous voltage is stored, and so on.

From the foregoing, it is seen that V7 and V8 serve as a switch, connecting the cathode of V5 with

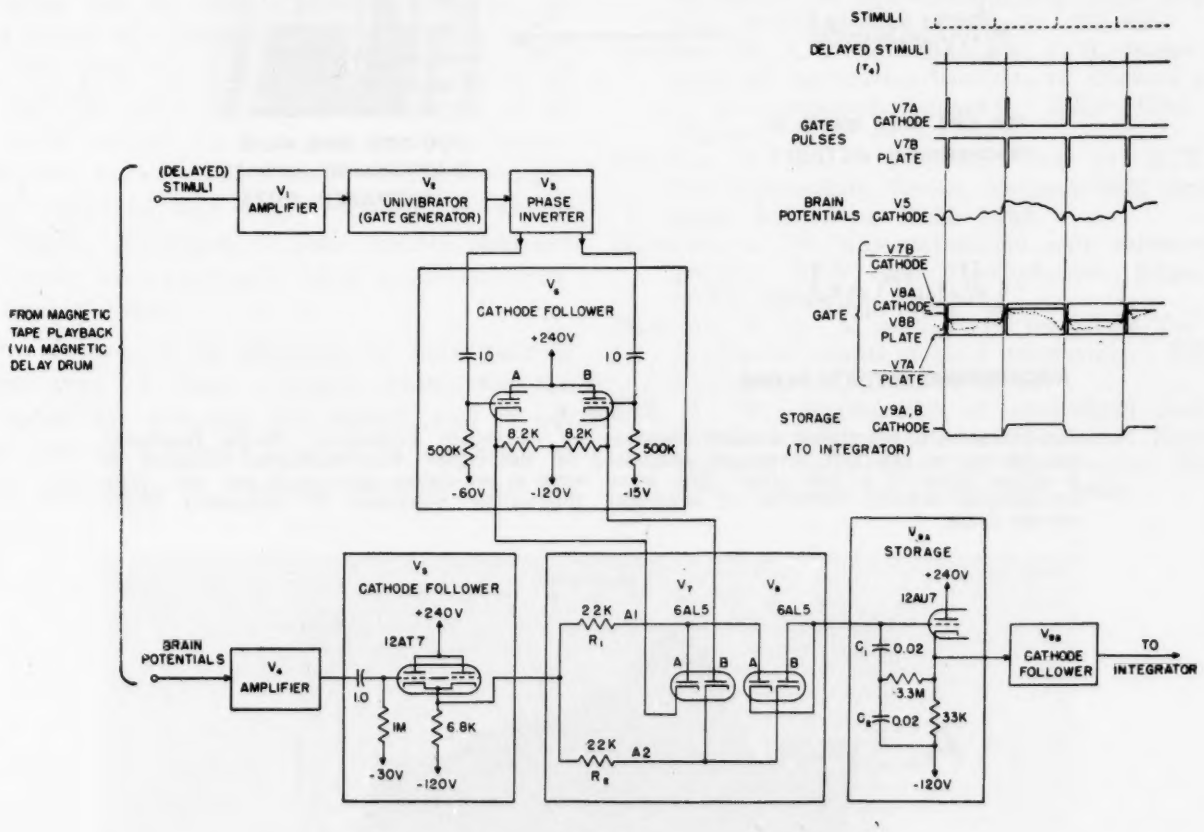


Fig. 2
Schematic and waveforms of gating-storage circuit.

relatively low potential at the plate of V7A, is at a lower potential than the cathode of V8A. The storage condensers (C1 and C2) are thus isolated from the fluctuating potentials at the cathode of V5.

At the appearance of a gating (i.e., delayed stimulus) pulse, the potentials at the cathodes of V6A and V6B are reversed, so that diodes V7A and V7B are no longer conducting: the plate of V7B is now at a lower potential than the cathode of V7B, and the cathode of V7A is at a higher potential than the plate of V7A, (the maximum signal out of V5 during the gating pulse not being large enough to start conduction in either section). With the shunting the storage circuit at the incidence of gating pulses, and isolating the storage circuit from the cathode of V5 in the absence of gating pulses.

The storage condensers C1 and C2 are arranged so that feedback obtained from their center-tap to the cathode of V9A compensates, within limits, for leakage of the stored potential (Chance 1949). The output step-function available at low impedance from the cathode follower V9B, is fed to the Miller integrator for obtaining the average at the particular delay for the series of stimuli. The result is recorded on an Esterline-Angus graphic milliammeter (1 milliampere full scale).

The clarification obtained by averaging a number of mock responses of constant amplitude amid an unrelated fluctuating background, in a simulated experiment, is indicated in figure 3. On the left in this figure are shown, respectively, a single cycle of a 100 c/sec. sine wave, the same sine wave mixed with background noise activity of 20-400 c/sec., and of the same r.m.s. amplitude as the sine wave, and

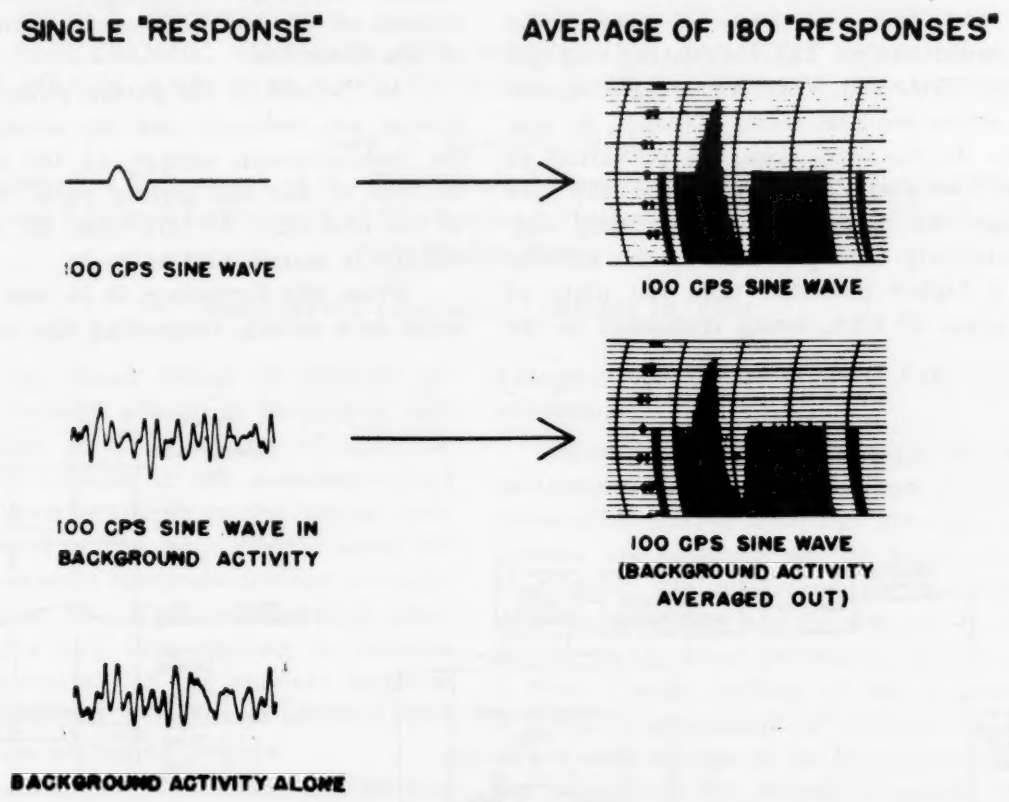

SINGLE "RESPONSE"
AVERAGE OF 180 "RESPONSES"
100 CPS SINE WAVE
100 CPS SINE WAVE
100 CPS SINE WAVE IN BACKGROUND ACTIVITY
100 CPS SINE WAVE (BACKGROUND ACTIVITY AVERAGED OUT)
BACKGROUND ACTIVITY ALONE

Fig. 3

Detection of a simulated evoked response by electronic averaging. Single responses are shown on the left, averaged responses on the right. The simulated response is a single cycle of a 100 c/sec. sine wave with a repetition rate of 5 per sec. The background activity consists of randomly fluctuating potentials of frequency range 20-400 c/sec.

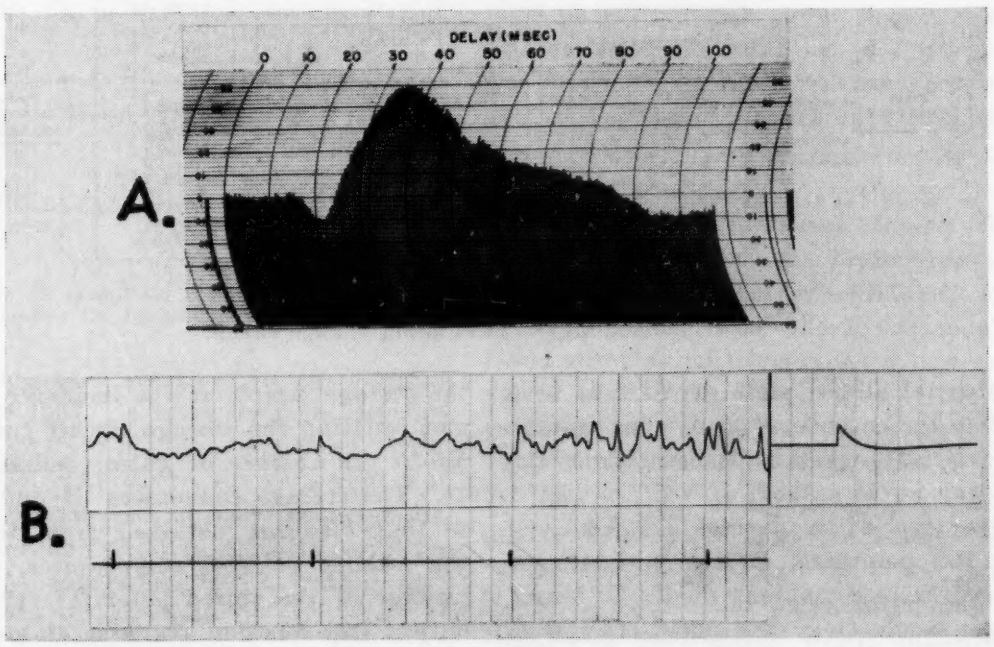


Fig. 4

Responses from the lateral gyrus of a cat under light Nembutal anesthesia to stroboscopic stimulation at a rate of 1 per sec. (A) Average of 200 responses. Delay after the stimulus in milliseconds (steps of delay 0.5 msec). (B) Sample of inked trace, showing four individual responses. Calibration 200 μV.

finally the background activity alone. On the right in the figure are shown the average of 180 mock responses of the sine wave alone, and of the sine wave mixed with the background noise activity. The average of 180 responses with noise shows the sine wave much more clearly than it can be seen in the individual responses, in which the sine wave is almost completely obscured by the noise. The theoretical gain in the signal-to-noise ratio, given by the square root of the number of responses averaged (Lee 1950), is approximately 13 (i.e. $\sqrt{180}$) in the example given above.

The average of 210 responses to stroboscopic stimulation at a rate of one per second, recorded from the lateral gyrus of a cat under light Nembutal anesthesia, is shown in figure 4. In this example, the steps of delay are 0.5 msec. From the figure, the latency of onset of surface positivity is seen to be 17 msec., the peak of surface positivity occurs at 22 msec. and the peak of surface negativity at 36 msec. A brief sample of the corresponding ink-recording is also shown. The clarity of the averaged response as compared with single responses is evident from the figure. Examples of some results obtained in clinical cases have previously been published (Brazier and Barlow 1956).

In the future, it is planned to substitute a phantastron type of delay (Chance 1949) for the magnetic drum for delaying the stimuli, and to use an endless loop of magnetic tape as an alternate to the present procedure of repeated rewinding of the tape. Details of these modifications will appear elsewhere.

The author is indebted to Dr. Mary A. B. Brazier of the Massachusetts General Hospital, and to Prof. Walter A. Rosenblith of the Massachusetts Institute of Technology, for their continuing interest and encouragement. In the completion of the system for correlation analysis of brain potentials, of which the equipment described here is a part, the author has enjoyed close collaboration with Mr. Robert M. Brown, of the Research Laboratory of Electronics, M. I. T.

REFERENCES

BARLOW, J. S. and BROWN, R. M. An analog correlator system for brain potentials. Technical Report 300, Research Laboratory of Electronics, Massachusetts Institute of Technology, **1955**.

BARLOW, J. S. and BRAZIER, M. A. B. A note on a correlator for electroencephalographic work. *EEG Clin. Neurophysiol.*, **1954**, *6*: 321-325.

BRAZIER, M. A. B. and BARLOW, J. S. Some applications of correlation analysis to clinical problems in electroencephalography. *EEG Clin. Neurophysiol.*, **1956**, *8*: 325-331.

CHANCE, B. Ed. *Waveforms*, Vol. 19, MIT Radiation Laboratory Series, McGraw-Hill Book Company, Inc., New York. **1949**.

DAWSON, G. D. Autocorrelation and automatic integration. *EEG Clin. Neurophysiol.*, Supp. No. 4, 26-37, **1953**.

DAWSON, G. D. A summation technique for the detection of small evoked potentials. *EEG Clin. Neurophysiol.*, **1954**, *6*: 65-84.

LEE, Y. W. Application of statistical methods to communication problems. Technical Report 181, Research Laboratory of Electronics, Massachusetts Institute of Technology, **1950**.

Reference: BARLOW, J. S. An electronic method for detecting evoked responses of the brain and for reproducing their average waveforms. *EEG Clin. Neurophysiol.*, **1957**, *9*: 340-343.

PRINTED IN CANADA

THE MEASUREMENT OF PHASE SHIFT IN ELECTROENCEPHALOGRAPH PEN RECORDERS

MICHAEL G. SAUNDERS, M.B.

Department of Physiology and Medical Research University of Manitoba and Department of Electroencephalography, Winnipeg General Hospital, Winnipeg, Canada

(Received for publication: October 29, 1956)

When any electrical or mechanical phenomenon is recorded, the recording system may fail to respond immediately. If the lag in response varies with frequency, distortion of complex waveforms may occur. With electrical phenomena the lag in response is described as phase shift and measured in degrees. Phase shift varying non-linearly with frequency produces phase distortion. Dawson and Walter (1944) and Cohn (1949) have shown how the form of a complex wave can be distorted by phase shift of its harmonics. Geddes (1951) has demonstrated variation in the position of the "spike" in a "spike and wave" with different degrees of phase shift. It is evident that the problem of phase distortion is of significance in electroencephalography.

In the amplifier the degree of phase shift at different frequencies may be readily determined. In the recording equipment the measurement is more difficult. No reference has been found as to the degree of phase shift or time lag introduced by electroencephalograph pen recorders, nor any accurate method of determining the degree of shift. To investigate the problem of phase shift and distortion in electroencephalograph pen recorders, two methods of measurement have been evolved and are presented.

METHODS

1. In this method use was made of Electrex kymograph recording paper. This paper has an electrically conducting surface so that a battery connected across a strip produces a potential gradient across it. For the experiments a 6 cm. long by 0.5 cm. wide strip of Electrex paper was cut in an arc of radius equal to the length of the pen being tested. The strip of paper was laid on plexiglass and clamped flat at either end (fig. 1). The pen tip, dried of ink, was placed on the Electrex paper so that it moved along the curve of the paper. A battery across the strip produced a potential gradient. The battery was center-tapped by two resistors. The potential difference between the pen tip on the paper and the center-tap of the resistors depended on the position of the pen. With the pens grounded, the potential between ground and the center-tap indicated the position of the pen on the paper.

To determine the phase shifts at different frequencies, the sine wave from a Krohn-Hite oscillator was attenuated and fed to the input of the electroencephalograph amplifier. Ten frequencies between 2 and 50 c/sec. were used. The pen deflections were set to approximately 2.0 cm. peak to peak. The center-tap of the resistors and ground were connected to the Y-plates of a DuMont cathode ray oscilloscope through its D.C. amplifier. The voltage feeding the pen coil was tapped, amplified by a D.C. amplifier and fed to the X-plates.

As the D.C. amplifiers produced no phase shift, the position of the oscilloscope spot represented the resultant of two potentials — that moving the pen and that representing the position of the pen tip.

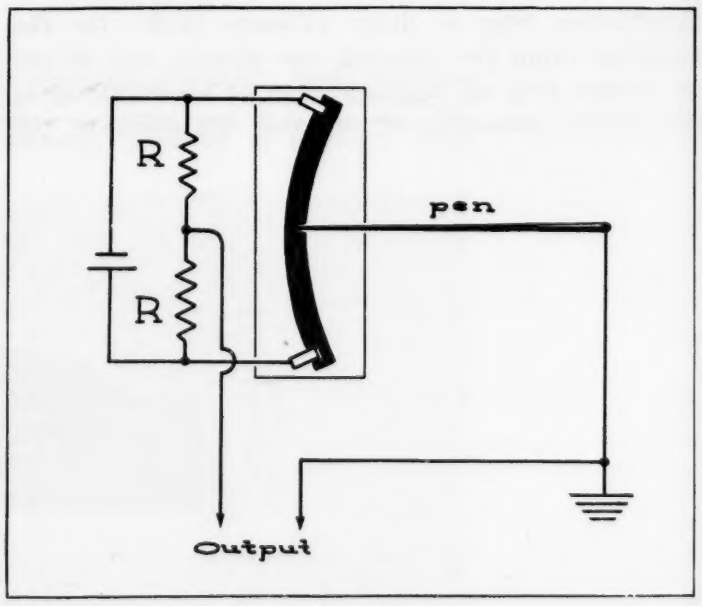


Fig. 1
First method of testing. The black curved strip is Electrex paper. The output feeds to the X-plates of an oscilloscope. The voltage moving the pens feeds the Y-plates.

With no phase shift between the potentials, a straight line running at 45° across the tube face appeared; this line opened to a loop as phase shift became apparent. Superimposed photographs of many oscillations were made at each frequency. An example of a loop at 30 c/sec. is shown in figure 2A. The photographs of the loops were enlarged and measured. From

these measurements the degree of phase shift was calculated using the formula quoted by Parr (1943)

$$\sin \phi = \frac{OP}{OQ}$$

where ϕ is the phase shift, OP the amplitude of the loop where it cuts the horizontal axis and OQ the maximum horizontal axis of the loop.

2. To check the results of the above method, a second technique was used. This method permitted the pen to write on moving paper with an ink flow to act as a lubricant. The arrangement is shown in figure 3. A dismounted pen was stuck onto a piece of plasticine and connected to an inkwell insulated from the recording unit. The pen was placed so that it lay under and behind the pen being tested. With no deflection on the pen being tested, the ink tracks of the two pens were made to coincide. The ink was electrically conducting so that the fixed and movable pens were joined by a conducting bridge when the two tracks coincided. When the pen was oscillating it made and broke contact with the ink bridge every time it crossed the track of the first pen. To detect the instant the moving pen crossed the ink bridge, a battery was connected through a resistor to ground and the inkwell of the fixed pen. Every time the moving pen crossed the ink bridge the circuit to ground was completed and a potential momentarily developed across the resistor. This potential was fed to the X-plates of the oscilloscope and appeared as a pulse. The sinusoidal voltage driving the pen was tapped and fed to the Y-plates. If the pen introduced no

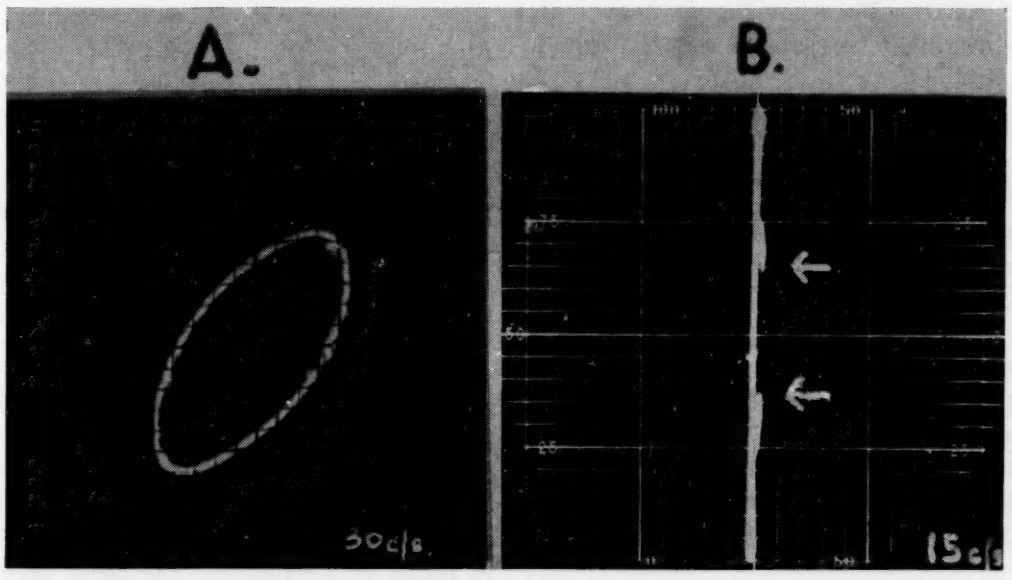


Fig. 2
(a) A Lissajous' figure produced by phase shift between the voltage moving the pen and the position of the pen tip.
(b) Time lag between the pen voltage crossing its mid-point and the pen crossing its mechanical mid-point. The pulses marked with arrows represent the instant the pen crosses its mechanical mid-point.
From these figures the degrees of phase shift can be calculated.

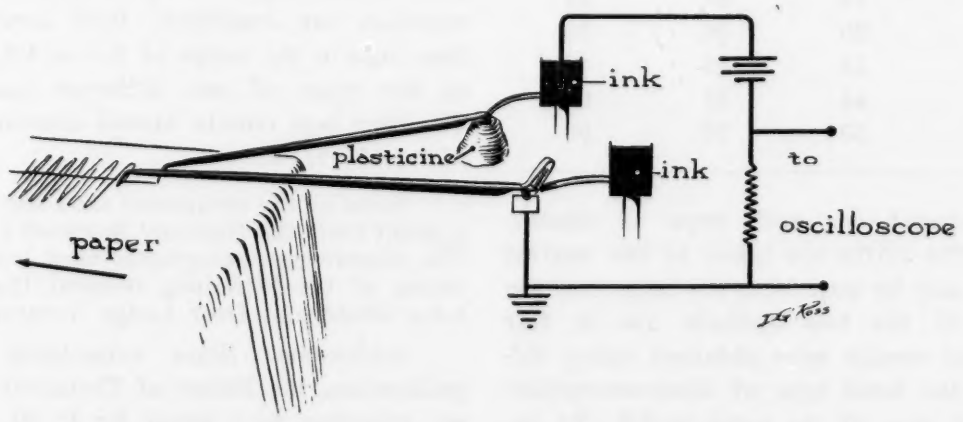


Fig. 3
Second method of testing. As the moving pen crosses the ink line of the fixed pen the pulses marked in figure 2b appear on the oscilloscope trace.

time lag, the mid-point of the sine wave driving the pen would coincide with the mid-position of the pen as it crossed the ink bridge and the pulse would appear in the middle of the oscilloscope trace. A lag between coil voltage and pen movement caused the pulses to appear after the coil voltage had crossed mid-point, that is on either side of the mid-point of the oscilloscope trace (fig. 2B).

Superimposed photographs were taken of the traces at the ten different frequencies. Measurements of the deviation from mid-point of the pulses were made from enlargements. The time lag or degree of phase shift at the different frequencies was calculated from the formula

$$\sin \phi = \frac{OR}{OS}$$

where ϕ is the phase shift, OR is the distance of the pulse from the mid-point and OS is the length of the trace from mid-point.

RESULTS

The experiments were conducted on two types of electroencephalographs, on different models of the same type and on different pens of the same models.

Typical results of estimations of phase shift at the ten frequencies are shown in table I. The two methods are compared for each type of electroencephalograph. The shifts are taken to the nearest whole number. It may be seen from the table that the results obtained by the two methods are in fair agreement. Similar results were obtained using different models of the same type of electroencephalograph or different pens of the same model. To demonstrate the time lags of the pen units, conversion from the phase shift figures of table I have been made and are shown in table II.

TABLE I

Phase shifts produced by pens of two different types of electroencephalograph. A and B are the different types. 1 is the method using the Electrex paper, 2 is the ink bridge method.

Frequency	Degrees of Phase Shift			
	A.1	A.2	B.1	B.2
2	—	2	4	3
4	4	4	8	6
6	6	7	10	9
8	7	9	14	14
10	9	—	17	18
15	17	16	23	24
20	26	20	30	30
30	37	33	45	45
40	46	44	57	65
50	63	58	75	90

TABLE II

Conversion of phase shift in table I to time lag.

Frequency	Time Lag in Milliseconds			
	A.1	A.2	B.1	B.2
2	—	2.8	6.2	4.2
4	2.8	2.8	5.6	4.2
6	2.8	3.2	4.6	5.0
8	2.4	3.1	4.8	4.1
10	2.5	—	4.7	5.0
15	3.2	3.0	4.3	4.4
20	3.6	2.8	4.2	4.2
30	3.4	3.0	4.1	4.2
40	3.2	3.0	4.0	4.5
50	3.5	3.2	4.2	5.0

DISCUSSION

At first sight the range of 3° to 90° phase shift shown in table I might suggest that the pen mechanisms are likely to produce serious distortion into the recording. However, expressing phase shift in degrees is merely a convenient method of expressing time delay in terms of frequency. The time lags of the pens at the different frequencies shown in table II demonstrate a nearly constant lag over the frequency range examined. It is now evident that a complex wave will have all its frequency components equally shifted and no change in temporal arrangement will occur. Provided other forms of distortion are not present, the pens produce time lag or phase shift but not phase distortion.

SUMMARY

Two methods of determining the degree of phase shift or time lag in the pens of electroencephalograph recorders are described. Both methods demonstrate time lags in the range of 3.0 or 4.5 msec., depending on the types of two different machines examined. The time lags remain almost constant over the range of 2 to 50 c/sec.

Some of the equipment used was provided through a grant from the National Research Council of Canada. The electroencephalographs used were in the departments of the Winnipeg General Hospital, the Manitoba Clinic and Deer Lodge Veterans' Hospital.

Addendum: Since submitting this paper for publication, the Editor of Technical Notes has drawn my attention to a paper by P. St. John Loe, *Proc. Electrophysiol. Tech. Assoc.*, 1954, *5*: 1, in which

a method of measuring total phase shift of amplifier and pen, using a stroboscopic light circuit, is described.

REFERENCES

COHN, R. *Clinical Electroencephalography.* McGraw-Hill Book Co. Inc., New York, **1949.**

DAWSON, G. D. and WALTER, W. G. The scope and limitations of visual and automatic analysis of the electroencephalogram. *J. Neurol., Neurosurg. Psychiat.*, **1944**, *8*: 119-133.

GEDDES, L. A. A note on phase distortion. *EEG. Clin. Neurophysiol.*, **1951**, *3*: 517-518.

PARR, G. *The cathode ray tube and its applications.* Chapman and Hall, London, **1943.**

Reference: SAUNDERS, M. G. The measurement of phase shift in electroencephalograph pen recorders. *EEG Clin. Neurophysiol.*, **1957**, *9*: 344-347.

PRINTED IN CANADA

AN ACTIVITY METHOD OF RECORDING GENERALIZED CONVULSIONS IN EXPERIMENTAL ANIMALS

CARL F. ESSIG, M. D. and HAROLD G. FLANARY, M.S.

National Institute of Mental Health, Addiction Research Center, PHS Hospital, Lexington, Kentucky

(Received for publication: October 8, 1956)

The method to be described has been used in determining the incidence of major epileptic seizures in cats during withdrawal from chronic barbiturate addiction. The technique may well be applicable to other studies where activity measurements are necessary. In experimental epilepsy, the method requires a reliable graphic indication of a specific episodic behavior pattern, the temporal occurrence of which can be calculated from a slowly moving, continuous record. Briefly outlined the apparatus utilizes movable cage floors, phonograph crystal pickups, power amplifiers, and ink recorders. The use of crystal transducers for activity recording (suggested by coauthor) has proven reliable over the past two years. In a recent report, Isaac and Ruch (1956) evaluate four activity techniques, none of which utilize this principle.

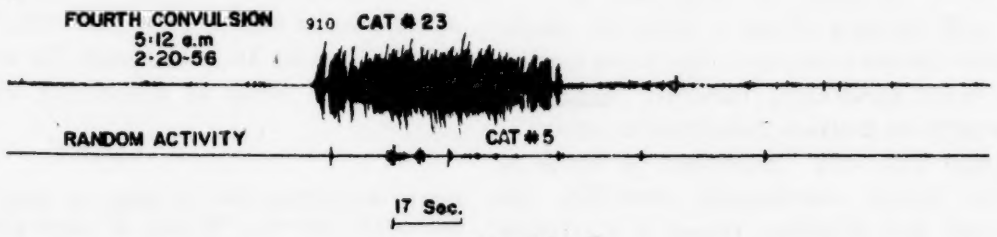


Fig. 1

Upper tracing demonstrates actual convulsion. Lower tracing, on another cat, is an example of properly attenuated random activity.

DESCRIPTION

Cage floors are mounted with compression or suspension springs which permit a ¼- to ½-inch distortion during a generalized convulsion. The details of floor mounting may vary considerably since cage sensitivity can be largely regulated at the amplifier stage. The limits of floor excursion are set by the durability of the crystal as regards its distortion tolerance. This aspect is partially regulated by using a curved section of piano wire 6 to 8 inches long between the floor and the fixed cartridge. The pickup is mounted close enough to permit the curved wire to absorb some of the distortion. Grass, Model II-B EEG power amplifiers boost the crystal output without using preamplification. The same model oscillograph, paper drive, and ink writer are used. However, the paper drive motor speed is reduced by a ratio of 60 to 1. Thus, a paper velocity as slow as 3 cm. per min. is available. Continuous recording for periods of several weeks is possible without using unreasonable amounts of self-folding, narrow gauge EEG paper.

The animal's random movements are dampened by adjusting the amplifier attenuator control. Cages may be "calibrated" by inducing an electroshock convulsion in an animal of similar size and noting the graphic configuration obtained on the record. Amplifier regulation is not extremely crucial because a characteristic pattern is obtained over a fairly wide range of gain settings if random movements are adequately attenuated first (fig. 1).

REFERENCE

ISAAC, W. and RUCH, T. C. Evaluation of four activity techniques for monkeys. *Science*, **1956**, *123*: 1170.

Reference: ESSIG, C. F. and FLANARY, H. G. An activity method of recording generalized convulsions in experimental animals. *EEG Clin. Neurophysiol.*, **1957**, *9*: 348.

PRINTED IN CANADA

SOCIETY PROCEEDINGS

DEUTSCHE EEG-GESELLSCHAFT

(The German EEG Society)

19-22nd of September, 1956, Berlin, Germany

Secretary: H. GAENSHIRT

Moorenstr. 5, Düsseldorf, Germany

1. The differential diagnostic delimitation of epilepsy in the electroencephalogram. — R. Hess, Zurich.

Epilepsy is defined as a state characterized by hypersynchronous potential variations which produce the attack. These manifest themselves in the EEG by high amplitude, high frequency short transients, by rhythmicity and paroxysmal occurrence. These changes can be generalized or focal. Among the generalized disturbances the morphology allows to draw certain conclusion on a statistical basis: the spike and wave discharges express a high probability for the presence of ''absences''. Furthermore, the majority of these cases are not related to a demonstrable organic cause and one has to reckon with a hereditary factor. The more the spike and wave complexes differ from the ideal form described by Jasper and Droogleever-Fortuyn the less certain these correlations become. A pattern almost as characteristic is seen in the form of ''hypsarrhythmia'' described by Gibbs. This is a disturbance which is most frequently seen in convulsive disorders of infancy with a bad prognosis. Otherwise any generalized disturbance suggests that the origin of the seizures is most likely not related to a focal process in one of the cerebral hemispheres. Such focal lesions, however, are suggested by focal EEG changes though the correlation here is not always certain. In general, an epileptogenic focus remaining constant over a longer period of time represents a good indication for a circumscribed organic lesion with disturbed function at its border zone. The wave form of the focal disturbances allows only to draw uncertain conclusions. An important correlation exists between the EEG pattern and the patient's age. In infants the hypersynchronous potentials are usually continuous and generalized, in older children intermittent and finally typically paroxysmal. In adults focal lesions are the most frequent ones. In children focal lesions account for about half of the cases but seem to have some preferential localizations according to the age of the patient.

2. The diagnostic significance of the EEG in cerebral tumours without papilloedema. — Krenkel, Cologne.

The author reports the EEG findings in 95 cerebral tumours without papilloedema. In 80 cases (84 per cent) circumscribed disturbances usually in the form of delta or theta waves were recorded. In 7 patients only a lateralizing diagnosis was possible. Two gliomas only showed generalized changes and in 6 cases the EEG was completely normal (1 meningioma, 4 epidermoid cysts, 1 osteo-lipo-fibro-chrondroma). When compared with methods using radio-opaque contrasts the EEG often shows in early cases a higher incidence of positive findings. From the differential diagnostic point of view the differentiation towards circulatory disturbances is often not possible in a single examination. However, with follow-up studies the differential diagnostic problem is almost always possible to solve. Since the benign cerebral tumours produce seizures in 80 per cent of the cases repeated EEG examinations in epileptics at short intervals are indicated in order not to overlook the opportune moment for an operative procedure.

3. Traumatic epilepsy in children and adolescents and their relation to epilepsy. — R. W. Meyer-Mickeleit and E. Schneider, Freiburg/Br.

Epilepsies after head injuries in childhood (birth injuries excluded) are clinically and electrographically different from the post-traumatic epilepsies in adults. An attempt to answer the question whether the childhood traumatic epilepsies can be legitimately incorporated within the group of residual epilepsies of other etiology, 65 epilepsies having occurred after confirmed traumatic cerebral lesions, were compared in matched age groups with 41 residual epilepsies having occurred after encephalitides and meningitides. Fifty-eight closed and 7 open head and cerebral traumas occurred at the ages of 7 months to 14 years. Twenty-six encephalitides and 15 meningitides occurred at the ages between 2 months and 14 years. At the time of the first EEG examination, the two groups of traumatic and inflammatory residual epilepsies were at about the same age level; one quarter were adults and three quarters children and adolescents. Clinically, the two groups of epilepsy due to trauma and to inflammatory cerebral lesions are not characteristically different: in each group in about 40 per cent of the cases neurological findings were present and in 60 per cent of the cases mental changes were found. About 50 per cent of the cases showed focal seizures. In the EEG the post-traumatic epilepsies of childhood showed somewhat more frequently generalized changes and epileptic potentials than the residual epilepsies after inflammatory cerebral lesions. Otherwise, the findings were very similar; in both groups about half of the cases showed focal changes and one third spike and wave variant forms in a focal or bilateral distribution. Three confirmed post-traumatic epilepsies of childhood showed 3 per sec. bilaterally symmetrical spike and wave discharges with clinical ''absences''. In the whole cases material ''absences'' (found in about one-fifth of the cases) were only found in combination with other types of attacks. The younger the child was when the cerebral

lesion occurred the more frequent were focal seizures, focal changes and epileptic potentials in the EEG.

From this investigation it can be concluded that the age at which the cerebral lesion occurs is a more important factor than the etiology in deciding which type of childhood epilepsy will occur. It seems therefore justifiable to consider childhood post-traumatic epilepsies as a sub-group of the residual epilepsies.

4. Concerning the problem of psychomotor epilepsy in childhood. — Niedermeyer, Innsbruck.

Forty-seven children with psychomotor epilepsy were investigated, 22 of whom were hospitalized the others were out patients. In all cases EEG findings are available. In 34 children the epilepsy was of a purely psychomotor type, in 13 there was a combination with grand mal. The cause of the seizures was usually undetermined and a positive history for heredity was found in only 5 cases. The neurological findings were most often normal. The pneumoencephalographic findings also were predominantly normal. The intellectual capacities were greatly disturbed in only 5 cases and in 7 cases intelligence was surprisingly good.

The electroencephalogram was only normal in 2 children. In 7 cases there was an unspecific dysrhythmia and in 38 cases specific epileptogenic changes were recorded. Among those, 14 children showed diffuse, 3 centrencephalic epileptic changes and in 21 cases the changes were of a focal nature. In these cases the focus was 18 times found in the temporal lobe and among those again 10 cases showed marked unilateral EEG changes.

This demonstrates how intimately the patho-physiology of psychomotor epilepsy is related to the temporal lobe. The mesial archicortical structures belonging to the rhinencephalon and which to-day are so much investigated from a neurophysiological point of view seem to play the major role in this seizure form.

It is necessary to distinguish as clearly as possible between psychomotor epilepsy and petit mal since this is also important from the therapeutic point of view. Only the true petit mal is improved by Oxazolidindion-therapy. The prognosis of psychomotor epilepsy is not as often assumed, generally bad.

5. Follow-up and EEG studies in pyknoepilepsy. — G. Paal, Freiburg/Br.

Among 90 children and juveniles with repeated frequent small attacks in whom at same time during the period from 1938 until 1950 a petit mal pattern was recorded in the EEG, 43 had a syndrome of pure pyknoepilepsy without grand mal attacks and 47 already suffered from generalized seizures. The 43 patients with pyknoepilepsy (24 girls, 19 boys) were followed-up and re-examined 6 years later at the earliest and 17 years later at the latest. *Fourteen of these patients had become seizure free, 12 now had generalized attacks and 12 still had unchanged minor attacks.* With five patients contact could not be renewed. The patients in whom major seizures had appeared were predominantly male (8 male and 4 female), the group of the unchanged petit mal cases (9 females and 3 males) and those having become seizures free (9 females and 5 males) were predominantly female. Generalized attacks appeared at the earliest 3 at the latest 10 years after the beginning of the disease whereas freedom from seizure occurred at the earliest 3 and at the latest 17 years after the beginning of the disease. Changes in the generative system (puberty, menarche, pregnancy) produced some changes in the clinical picture in most of the cases. In some this was represented by arrest of seizures in others by the onset of major attacks. Still others showed during menstruation a clear increase of seizure incidence. The clinical pattern gave no clues allowing to make a clear prognosis. It seems, however, that late onset of the disease, a demonstrable organic cerebral damage, a tendency to frequent attacks early in the morning or personality changes, indicate an unfavorable course of the disease. The presence of hereditary factors does not exclude a favorable course. The form of the petit mal discharges in the EEG did not allow any prognostic conclusions, since the same patterns were found when later freedom of seizures occurred as well as in the cases which showed transition to grand mal. However, it seems that a great frequency of occurrence and spontaneous occurrence of petit mal attacks is rather a prognostically favorable sign. In cases where later major attacks occurred a minor attack could often only be obtained with hyperventilation and in almost all cases which meanwhile became free from attacks, such minor discharges were already seen spontaneously at rest. Signs pointing to a rather unfavorable course are isolated spikes, constant focal changes and severe generalized EEG disturbances. In 5 patients free of seizures clinically and in which an EEG follow-up study could be obtained, 2 had a normal EEG, 3 showed some isolated waves with a steep wave front among which was a patient who had been seizure free for 17 years, whereas another patient who had been seizure free for 5 years showed groups of atypical epileptogenic potentials.

6. Focal changes and EEG in petit mal epilepsy. — A. Calderon and G. Paal, Freiburg/Br.

In 144 patients with typical petit mal and 3 per sec. spike and wave discharges in the EEG, 65 per cent showed no focal changes, 21 per cent showed changes suggestive of a focal abnormality of shifting foci and 14 per cent showed constant circumscribed EEG foci. Eighty-two patients had major and minor attacks and 62 only minor attacks. Temporal lobe and Jacksonian epilepsies were excluded in this study. Among 50 patients with focal changes in the EEG 30 had minor and major attacks and 20 only minor attacks.

The age of onset of the disease in the patients with major and minor attacks was definitely higher than in those with only minor seizures. In 26 patients an exogenous cause was detectable but in 24 there was no such indication. When comparing the EEG with the clinical and X-ray findings there was a good correlation. The minor attacks were always correlated in the EEG with typical 3 per sec. paroxysmal discharges which only in 10 cases showed an inconstant focal onset or in 12 cases a more constant asymmetry. Besides the 3 per sec. discharges there were also 2 per sec. variants, seen 14 times during the minor attacks in younger patients below 10 years, and 7 times in an isolated focal distribution in different age groups. Focal changes were only found in between the attacks mostly in the form of steep waves, isolated spikes or typical or unilateral paroxysmal waves and their variants. Only 16 had delta foci and focal dysrhythmias. Ten foci were found occipital and 10 in occipito-parietal regions, 2 in parietal areas, 2 in temporal regions, 5 in temporal basal regions, 4 in precentral areas and 2 in frontal regions. Fifteen patients showed dysrhythmias over one hem-

isphere without circumscribed focus. The relatively frequent occurrence of focal changes in the EEG (35 per cent of all cases of petit mal) and of exogenous cerebral damage in those focal cases (52 per cent) is in contradiction to the view that bilateral 3 per sec. spike and wave discharges are signs of idiopathic epilepsy. It is more likely that the EEG form of petit mal is a reaction of the infantile cerebrum to any epileptogenic irritations which can act on various places within the brain.

7. The significance of electroencephalography for the treatment of epilepsy. — Landolt, Zurich.

Starting from the assumption that in principle in treating epileptic patients the normalization of the EEG is a desirable goal, the application of this method and its usefulness in relation to this goal are reviewed, always assuming that a pathological EEG is the starting point of such an investigation. One of the premises under which such a study has to be carried out is a profound knowledge of the EEG in healthy persons, in which normally some asymmetries and focal changes may be found. Equally important is adequate knowledge of those EEG changes which are not necessarily in relation with the disease, such as for instance, maturational disturbances and retardations. There are types of waves which are not apt to be influenced by anti-convulsive medications and an attempt to do so could lead to administration of anti-convulsive medication in too high and wrong dosages.

The correlation between the improvement of the convulsive disorder and of the EEG changes is in general satisfactory. Therefore especially in patients with a rare incidence of attacks and frequent occurrence of abnormal waves, this method represents a useful indication for the physician and for the patient to evaluate the effect of treatment.

Less consistent is the correlation between the EEG and the episodic phenomena of epilepsy such as twilight states psychotic episodes and changes in mood in which the electrographic pattern can become nearly normal in certain cases even during exacerbation of the clinical symptoms.

Only rarely is the correlation simple and direct for the chronic mental and neurological changes in epilepsy. A normal EEG with a continued state of defect (deficatory syndrome) can be the expression of a primary or secondary loss of substance and thus, except for maturational processes in children, no further improvement can be expected. On the other hand a pathological EEG allows to expect the presence of an, at least partially reversible, dysfunction producing the electrographic disturbance.

The more detailed knowledge of epileptogenic patterns and the increase of the number of anti-convulsive drugs give rise to the hope that these drugs could be especially suited for special forms of the disease. Thus, general rules for the administration of these drugs were established though in many cases one is still forced to rely on empirical methods necessitating experimental trials in order to find out which are the optimal combinations and dosages of the drugs to be used. The recognition, maintenance and restoration of the individual psycho-physiological balance (for instance EEG and psyche) is often very important. In no case is one entitled to exclude a brain tumor or a destructive lesion when the EEG pattern becomes normal.

8. The importance of the EEG for the operative indication in symptomatic epilepsies. — von W. Götze, Berlin.

On the basis of a statistical analysis computed from findings published in the literature and on the basis of own observations it was demonstrated that after excision of meningo-cerebral scars in focal epilepsies a considerable parallelism exists between the persistance of epileptiform disturbances and the reappearance of seizures. Cases which remained seizure free over years usually were also free of epileptogenic changes in the post-operative records. An almost 100 per cent correlation between post-operative freedom from seizures and improvement in the EEG was found in cases with hemispherectomies.

In focal epilepsies cases with localized spikes showed a more favorable prognosis than those with localized slow waves. Generalized occurrence of slow disturbances impaired the post-operative prognosis. In temporal lobe epilepsies the operative success is impaired as soon as there are bilateral epileptogenic foci in the EEG. It has been pointed out that corticography, which showed in 80 per cent of the cases localized epileptogenic changes, is of great importance in symptomatic epilepsies in order to delineate the localization of the focus. Especially in the residual epilepsies, in which clinical signs for focal localization were absent, a constant EEG and corticographic localization can give the only indication for an operative procedure. Even after an open cerebral trauma which lies back many years the electroencephalographic investigation is the only method which gives an indication for changes in the functional state in the vicinity of the scar, as they sometimes occur in the course of encephalitic processes. Often in these cases with large scarring partial removals can be carried out successfully.

The EEG criteria considered necessary to justify operation are as follows: (1) the clinical localization and the localization of the EEG focus must coincide; (2) when the clinical findings are negative the EEG localization has to be controlled by repeated examinations and if necessary by findings obtained with the help of some activation procedures; (3) operation seems contraindicated when there are generalized slow disturbances in the EEG and in temporal lobe epilepsies with bilateral foci; (4) in cases in which hemispherectomy seems indicated, bilateral EEG changes are not a contraindication for operation; (5) with the help of corticographic records it is possible to localize the electrographic epileptogenic focus. Often this allows even in large scars partial removals with successful results; and (6) in order to improve the findings during corticography it is desirable to carry out an EEG examination on the day of operation and to operate only when the EEG is active. Thus it can be hoped that the incidence of positive corticographic findings can be increased.

9. Excitation and excitability. — E. Schütz and H. Caspers, Münster.

The functional organization of the central nervous system disposes of various physiological mechanisms of regulation which prevent synchronized mass discharges even when there is a massive synchronized excitatory input as for instance during arousal. One of these mechanisms is represented by the continuous oscillations of the central excitatory state which follow the rhythm of the spontaneous potential oscillations. Besides this, the manner in which the central nervous

system deals with incoming stimuli plays an important role in the prevention of development of seizure discharges. Each stimulus produces activating effects, but besides this, also inhibitory phenomena. These are partially structurally determined (e.g., on- and off-elements) and partially are dependent upon dynamic factors such as the activity of the stimulated substratum before the stimulation took place and the parameters of stimulation used. Owing to a temporal and spatial dispersal of the facilitatory and inhibitory processes, considerable shifts in the balance of excitation are prevented (Jung and coll.). In the cortex the tendency to synchronization of excitation is not only influenced within a large degree by local regulatory mechanisms but also by the state of activity of the unspecific projection mechanisms of the brain stem reticular formation. According to results obtained by direct threshold measurement (Caspers) the convulsive excitability of the cortex diminishes by about 20-30 per cent below the average level during wakefulness when the reticular excitatory state is enhanced by direct, peripheral or cortical stimulation. Conversely this cortical convulsive excitability increases by about the same amount above the initial value, when the activity of the unspecific projection system is inhibited by spontaneous or electrically induced sleep, light anaesthesia or after often repeated central or peripheral stimulations. These results suggest that the development of convulsive activity can only in rare cases, if in any, be related to the disturbance of a single inhibitory factor at the site where the convulsive activity develops.

10. Conditions for the development of seizure activity in experimental epilepsy. — R. Jung, Freiburg/Br.

The author discusses the development of local seizure activity in the iso-cortex in response to electrical stimulation and strychnization. The experiments were based upon recordings from single neurones and of the surface activity recorded with conventional electrodes. Development of epileptic convulsive activity presupposes disturbances of the normal regulation of cerebral activation and of braking mechanisms. On the basis of microelectrode records taken in regions of the cortex with afferent input, three physiological anti-convulsive braking mechanisms of neurones can be differentiated, which in the normal brain, prevent the development of the convulsive activity: (1) stabilizing activity of the A-neurones which are not influenced by afferent stimuli; (2) the balance of excitation and inhibition in the activity of the neurones influenced by afferent stimuli — (*a*) simultaneous and reciprocal excitation and inhibition of several antagonistic neurones, (*b*) consecutive pre- or post-excitatory inhibition of the same neurone — (3) inhibition of over-excitation characterized by diminution of the living frequency of the neurones in response to high frequency afferent stimulation.

After electrical stimulation fundamentally different reactions to low and high frequency excitation are noticed: single stimuli or low frequency stimuli below a repetition rate of 8 c/sec. produce constant inhibitory pauses with secondary activation but no epileptiform discharges. With higher frequency stimulations from 10-100 c/sec. the neurones become able to discharge also during the inhibitory pause and are apt to precipitate in every normal brain an epileptiform discharge, provided that the duration and intensity of the stimulation is of sufficient magnitude. Before the convulsive stage the microrhythms show a prolongation of the primary wave and the single neurones show repetitive discharges without prolonged inhibitory pauses.

After strychnine administration there is a similar prolongation of the primary wave with enhancement of the secondary waves and the single cells show the transition from a single or twin discharge to repetitive discharges. It is postulated that the single electrical stimulus produces a short-lived summative facilitation and a more prolonged inhibition. It is also assumed that the inhibitory mechanism fatigues with rapidly repetitive stimuli and is paralyzed by strychnine.

11. The spread of epileptic excitation. — E. Müller, Dortmund.

The spread of the after discharges outlasting the application of chemical or electrical stimuli, which are considered characteristic for epileptic excitation, was investigated in unanaesthetized, but immobilized rabbits. It was found that epileptogenic discharges can primarily be induced only from the old cortex, especially from Ammon's horn, from the neo-cortex from certain parts of the diencephalon such as the anterior thalamic nucleus and from the amygdala. It is still uncertain whether the nucleus caudatus has to be added to the list of the structures from which convulsive discharges can be directly elicited. These structures can be considered as potential foci of an epileptogenic discharge. The more caudal parts of the brain do not have the aptitude to act as a focus. They are acting upon the epileptogenic areas as modulators. Strong stimuli applied to these modulators can produce an outlasting after discharge of higher structures. The abnormal excitation spreads from the primarily epileptogenic area into other regions via anatomical pathways. However, the structural relationships are not always respected, especially they never are respected for a long period of time. Due to changes in excitability new ordinarily not involved pathways, become opened to the spread of epileptic discharge. From a certain moment on the epileptic excitation becomes generalized and it is not possible to pinpoint the area the involvement of which would be crucial in the generalization process. Though the structural relationships should not be neglected it is necessary to point out that the diffusion of the epileptic excitation can only partially be regarded as a structural problem.

12. Cerebral circulation oxygen supply of the brain and epileptic attacks. — H. Gänshirt, Düsseldorf.

Cerebral circulation and oxygen uptake of the brain are normal in idiopathic epilepsies in between attacks (Kety and Schmidt, Brobeil and co-workers, Gänshirt and co-workers). Diminution of cerebral circulation and oxygen uptake in the interval between seizures in patients with epilepsy due to tumours or due to increased vascularization in arterio-venous aneurysms are determined by the underlying disease. A comparison of tumours of the same histological type and similar localization with and without symptomatic epilepsy shows that tumour patients with seizures show a significantly lower cerebral circulatory rate than is found in normal individuals, but a statistically validated higher rate of cerebral circulation and cerebral oxygen uptake than tumour patients without epileptic seizures (Gänshirt). During the attack cerebral circulation and oxygen uptake of the brain increase (Gibbs; Lennox and Gibbs; Penfield and co-workers; Geiger and Magnes; Schmidt, Kety and

Pennes). The cause for the increase of circulation is increase in CO_2 tension, formation of lactic acid and perhaps liberation of acetylcholine. The diminution of glucose and the high energy phosphates as well as the accumulation of anorganic phosphate and of lactic acid during the attack indicate an increase of liberation of energy and of anaerobic glycolosis. The cerebral circulation increases during the epileptic attack by about 60 per cent and the oxygen uptake of the brain increases by about 100 per cent (Kety and co-workers). The output of electrical potentials as measured from scalp records increases by about 12 times during the electro-convulsive seizures (Meyer-Mickeleit) and when recorded directly from the surface of the brain the increase is about 50 times the resting value (Jung). The output of electrical potentials is not proportional to the aerobic energy production because it is dependent also upon the degree of synchronization and because the anaerobic energy production cannot be calculated from the oxygen uptake. If the doubled oxygen uptake of the brain during the seizure is used in Krog's formula and applied to a standard tissue cylinder of cerebral cortex and if furthermore one considers, when doing so, that the oxygen reserve (Opitz and Schneider) of the brain is exhausted due to the apnoea and the increased oxygen consumption by the convulsing musculature during the generalized epileptic attack, one can compute that the oxygen tension in the cerebral tissue during a generalized seizure is locally diminished below 19 mm Hg. Despite the increase of circulation the cerebrum during an attack becomes deficient in oxygen. Thus the conditions are fulfilled for the development of anatomically detectable lesions of the tissue. Experimental investigations proved that strychnine discharges and electro-convulsive seizures can be shortened by lack of oxygen and can be prolonged considerably by supplying oxygen (Kornmüller and Noell; Gellhorn and Hymans; Ruf). With complete arrest of circulation (occlusion of the aorta or pulmonary artery) and after disappearance of the electrical spontaneous activity the brain can still be induced to produce convulsive activity by applying a diffuse electrical stimulus (Gänshirt). The brain is still therefore able to convulse even without oxygen. Lack of oxygen in the brain can precipitate seizures because the nervous tissue becomes hyperexcitable by the depolarization induced by the hypoxia (Lorente de Nó). Anoxia produces inhibition of convulsive activity because of lack of energy and because the tissue becomes unexcitable. The degree of the hypoxia and the intensity of the pathological stimulus together with regional differences in the susceptibility to lack of oxygen (high altitude convulsions) determine whether and when lack of oxygen will produce convulsions.

13. Chronic focal epilepsy in animal experiments. — STEINMANN, Cologne.

In experimental research of epilepsy the standard procedure to produce chronic epileptogenic phenomena is the Kopeloff method. Depending upon the species of animals used, 0.05-0.1 cc. of alumina cream applied to the cortex or to subcortical nuclei are necessary to produce manifest seizure phenomena which occur for the first time after a latent period of several weeks to several months. Most studied, so far, were the convulsive manifestations produced by such lesions in the sensory motor region of the cortex, as well as in the temporal cortex and in certain sub-cortical areas. The behaviour disturbances in temporal and occipital epileptogenic lesions described in the literature were briefly summarized by the author. More closely described was the course of the bioelectrical changes in the region of the lesion, in the remainder of the cortex and in certain sub-cortical areas. Especially the variability of the temporal foci was analyzed closely because of their great importance for clinical problems. With the aid of several experiments with removals which were checked on model experiments the possibilities and limitations of a successful surgical therapy were finally discussed.

14. Synchronization phenomena of neighbouring intracerebral nerve cells. — R. VON BAUMGARTEN and K. P. SCHAEFER, Göttingen.

The action potentials of neighbouring nerve cells in the cortex and in another series of experiments in the reticular formation of the lower brain stem in the cat were studied with extracellular micro-electrodes. The electrical phenomena were displayed on the cathode ray oscilloscope and photographed at a high film speed. With this method the following temporal relationships between single discharges of neighbouring ganglionic cells were found:

(1) Loose coupling, i.e. not always constant but statistically validated relationship of firing of two or several units.

(2) Rigid coupling, i.e. constant synchronization of two or several units.

(3) When the firing frequency is forced to increase due to electrical or pharmacological influences, there are continuous transitions from loose to rigid coupling.

(4) According to the rules of relative coordination developed by von Holst, it is the unit with higher discharge frequency which exists a ''magnetizing effect'' upon the less frequently discharging unit and therefore determines its timing of discharge.

(5) The thus synchronized unit can, according to its own propensity to discharge fire within its assigned discharging period either immediately before or immediately after the synchronizing unit.

The last finding together with other observations demonstrate clearly that within a period of at least 30 msec. before and after the discharge of a rythmical unit, the propensity to discharge increases in its extracellular environment in an area which includes that occupied by neighbouring cells. These rhythmical variations of the local conditions favouring discharge of nerve cells act independently from the non-synaptic time relations and can be considered as late effects of a preceding discharge or as effects exerted by a third element acting as a pace-maker.

Extracellular synchronizing phenomena favour the hypothesis of von Gerard and Libet and Bremer and other authors according to which in epileptic convulsive activity one has to reckon with non-synaptic ''ephaptic'' spread of convulsive activity besides the proprogation mediated by nervous pathways.

15. Convulsive discharges of single cortical neurones. — O. CREUTZFELDT, Freiburg/Br.

Micro-electrode records of convulsive discharges of single cortical neurones were demonstrated together with ''macro-records'' of the EEG. The convulsive discharges were precipitated by electrical stimulations at 10-50 c/sec. applied to the cortical surface close to the micro-electrode. Often the convulsive discharge of single neurones start only 100-500 msec. after the end of stimulation and only with long durations of these stimulations were seen to start already during

stimulation. In convulsive discharges of a tonic-clonic sequence one observes first that all neurones show simultaneous continuous activity with discharges between 10-50 c/sec. rarely with higher frequency discharges up to 300 c/sec. which are not co-ordinated with each other. In the EEG one observes first only small waves with a frequency of 10-50 c/sec. and later larger convulsive potentials. After the tonic stage there is in certain cases a stage of ''clockwork'' activity, characterized in the EEG by very regular epileptogenic potentials at 10 c/sec. The single neurones show unitary discharges synchronized with the EEG which occur singly or in short bursts of 2-5 discharges. In the following clonic stage the EEG shows either single large epileptogenic potentials or short bursts of potentials with increasing intervals. The single cell discharges appear synchronously with these EEG potentials in high frequency bursts with discharge frequencies ranging from 50-300 c/sec. and even reaching sometimes 700 c/sec. The duration of these bursts is different with different neurones and they may consist of 2-20 discharges. Towards the end of the convulsive period the frequency of the bursts and of their single discharges diminishes. After the paroxysm there is quiescence for at least 10-20 sec. Until a normal discharging rhythm of the single neurones is resumed at least 1 min. elapses. There are numerous deviations from this ''typical'' course of convulsive events as illustrated by the author with several examples. Two mechanisms of altered neuronal activity during the cortical convulsive attack have to be considered: (1) a pathological increase of activity of the single neurone, and (2) a tendency to abnormal synchronization. The enhancement of activity of the single elements is preponderant during the tonic stage and therefore the single neurones discharge in an uncoordinated way during this phase. On the other hand in the clonic stage synchronization with grouping of discharges predominates.

16. Investigations concerning cerebral metabolism during electroencephalographic convulsive activity and in petit mal attacks. — Heyck, Zurich.

In 2 female patients with epilepsy and easily induced generalized convulsive activity in the EEG it was possible to determine the cerebral arterio-venous oxygen difference with the method of Haldane continuously before and after the attacks. The first patient showed, with little Cardiazol, multiple spike and wave patterns without clinical manifestations of a duration of more than 10 min. The second patient after stroboscopic stimulation without any use of drugs or hyperventilation showed during 5 min. almost uninterrupted by clinical ''absences'' with associated typical 3½ c/sec. spike and wave discharges. In both patients the resting electroencephalogram until the beginning of the provocation of these phenomena was entirely normal. The first case showed a small increase of arterio-venous oxygen difference which was within normal limits and in temporal relationship with the application of the Cardiazol. In the second case, a very minute increase of the arterio-venous difference receded, already during the attack, to the pre-seizure level. This indicates that there was only a small increase of cerebral metabolism which was in no quantitative relationship with the increase of electrical activity as measured in the EEG. Cerebral anoxemias and their sequelae in epilepsy are therefore unlikely to be related to an increase in activity of cerebral neurones as suggested by the EEG and as assumed by Jung and others, but they are apparently related to those circulatory disturbances which only occur with tonic-clonic seizures (Scholz). The hypersynchrony is no measure for the increase in cerebral metabolism. The author demonstrates the EEG records, the data of the measurements of the arterio-venous differences and their temporal relationships.

17. "Expansive" psychoses in epilepsy with EEG changes. — Faust, Freiburg.

(Abstract not submitted.)

18. Investigations of free amino acids and peptides with high voltage electrophoreses with special consideration of epilepsy. — Hemmer, Freiburg.

With the aid of high voltage electrophoresis modified for the clinical use by Heilmeyer and Clotten it is possible to investigate the substances responsible for the non-protein nitrogen in the blood, especially the free amino acids and the peptides. Animal experiments are discussed in which the free amino acids and peptides were investigated after continuous cortical stimulation and after electro-shock with uninhibited and inhibited motor discharge. The results show a marked shift of the amino acid spectrum even when motor discharges are suppressed. Especially an increased break down of dicarbonic acids and glutathions is remarkable under those circumstances.

19. The importance of the value of background cerebral activity related to vegetative tonus for the cortical EEG. — H. Hippius, Berlin.

In stimulation experiments with strychnine performed on the cerebral cortex of the rabbit, Janzen and co-workers showed a topical differentation of cortical epileptogenic potentials in the electrocorticogram. With this experimental technique it is possible to demonstrate not only a relationship of the characteristics of the convulsive activity dependent upon the locus of stimulation, but also dependent upon the frequency of the background rhythms. With intermediate frequencies groups of convulsive single discharges at the locus of stimulation occur for instance in a precentral strychnine focus. With increase of the frequency, the number of single convulsive discharges belonging to a particular group increases and the number of these convulsive single discharges per unit of time rather decreases because the intervals between the groups of single convulsive discharges become more prolonged. With pronounced increase of background frequency isolated electro-convulsive discharges may occur. If background frequency goes below normal range, the groups made up of single convulsive discharges disintegrate together with a concomitant increase of the number of single convulsive discharges per unit of time. With even more pronounced decrease of background frequency the single convulsive discharges become more and more rare until they finally disappear completely. In these experiments it was seen that it is irrelevant whether the changes in background frequency are of spontaneous origin or artificially produced, e.g. by drugs.

Since the changes in background frequency are considered as the expression of changes in the vegetative tonus it can finally be concluded that besides a topical differentation the background activity, reflecting the vegetative tonus, plays an important role in the elaboration of cortical convulsive potentials.

20. Endogenous epilepsy of the rat and its response to anticonvulsive medication. — QUADBECK, Heidelberg.

In numerous rat strains one can observe a high incidence of epileptic seizures. These occur spontaneously and are especially easily precipitated by auditory stimuli. There is a hereditary disposition for these convulsions and it is therefore possible to breed rats with a high incidence of seizures. In the course of two years, the incidence of seizures in a strain could be increased by inbreeding from 52 per cent to 56 per cent. Besides the hereditary factor the propensity to convulsions of the single animal is influenced by several external factors such as nutrition, the weather and there is also a cycle of variation during a 24 hour period. The convulsions can be suppressed for prolonged periods of time by the use of anti-convulsive drugs. A single administration of 200 mg. substance/kg. body weight given by mouth protects 50 per cent of the experimental animals even with intense auditory provocation. With Zentropil protection lasts for 24 hours, with Mesantoin for 27 hours, with Mylepsin for 44 hours, with p-Brom-Nirvanol (Heyden S127) for 94 hours with Phenurone 9 hours and with Tridione one hour. There is therefore a considerable correlation between the anticonvulsive activity in the rat and the efficiency to control grand mal seizures in man. Since there is no such parallelism for electroconvulsive seizures as well as for the chemically induced attacks, it is probable that the spontaneous epilepsy of the rat perhaps is more closely related to grand mal epilepsy in man than those forms. It is therefore considered that such rats are good subjects for model studies on epilepsy. (Film)

21. Excitatory pattern in pre-central foci. — K. SCHMALBACH, Cologne.

The author reports on experiments carried out on 23 cats with chronic epileptogenic foci according to the method of Kopeloff and on 10 cats with focal discharges produced by electrical stimulation or strychnine application. All these foci were located in the motor cortex. The recordings from the cortex and depth recordings obtained with needles implanted in sub-cortical structures showed typical excitatory patterns in different stages of development of the epilepsy, the motor manifestations of which often showed the picture of epilepsia partialis continua. The acute experiments which were performed with the same recording technique shed light upon a completely different aspect of epilepsy since in this form the counter-regulations typical for chronic processes are absent. Patterns with typical formations of sharp waves in the region of the focus were seen in records taken from the bone and the lability of the situation in the brain before the outbreak of an attack was demonstrated. The author demonstrates with different depth recordings sub-cortical discharges in rostral parts of the brain which often show a much more intense convulsive activity and may or may not be synchronous with the cortical discharges. In these cases there is no participation of the amygdaloid nucleus in the convulsive activity. The author also cautions against the overrating of the phenomena derived from inspection of the actual record.

22. Chlorpromazine sleep as an electroencephalographic activation method. — D. BENTE and T. ITIL, Erlangen.

Previous electroencephalographic investigations have suggested that chlorpromazine (Megaphen, Bayer) fosters dysrhythmic activity and activates discharges of epileptogenic potentials. Chlorpromazine sleep was, therefore, used as a diagnostic provocation method. Sleep induced by chlorpromazine is very similar to physiological sleep. However, the particular effect of the drug is still clearly recognizable by the tendency to rapid increases in amplitude, slowing of the rhythms and synchronization of grouped discharges. These peculiarities are already seen before the patient goes to sleep and are still recognizable during sleep. Chlorpromazine exerts its activating effect especially upon mild dysrhythmias, minor sharp waves and sequences similar to convulsive activity. These phenomena are accentuated in direction of a more unequivocal epileptogenic manifestation. The advantage of chlorpromazine activation is due to the fact that relaxation and sleep can be obtained in 86 per cent of the cases with almost none of the disturbing pharmacological side effects as seen with barbiturates. For the activation of circumscribed cortical foci this method is however surpassed by other activation procedures. For the EEG diagnosis in children chlorpromazine administration is a good preparatory measure and easy to handle.

23. Activation by Megaphen and Cardiazol. — E. W. FÜNFGELD, Marburg.

Based on previous investigations (published in the Arch. Psychiatr. Zlsehn Neurol., vol. 194) the present one was carried out. The method consisted of mixing 2 cc. equal to 50 mg. Megaphen with 100 cc. equal to 300 mg. of Cardiazol (according to the body weight of the patient) with 15 cc. of an isotonic blood salt solution (Jonosteril). The injection was slow at a rate of 1-2 cc. per min. As soon as recognizable changes appeared in the EEG the injection was discontinued. Immediately afterwards a short period of hyperventilation was induced. The anxious excitation which usually seizes the patient with Cardiazol injection alone does not occur due to the quietening effect of Megaphen. Both drugs together exert, as has already been shown, a summative activating effect upon the EEG.

Among the 17 patients reported in this series 9 times a more precise EEG diagnosis was possible. Four cases suffered from idiopathic epilepsy, 4 from focal epilepsy and once a theta wave focus was observed. Even during continued anti-epileptic medication an activation procedure is sometimes indicated in certain cases. With focal lesions without an increased tendency for seizures the method is also useful in giving more precise informations.

24. The hypnotic and sedative drug N-Phthalyl-Glutaminic-acidimid as a useful activator in electroencephalography. — A. WALKENHORST, Bochum-Langendreer.

The author points out to the large number of activating procedures in electroencephalography and to the limitations of each single method. With sleep activation the choice of the drug used for activation was discussed. It was thought that Contergan, a glutaminic acid derivative with a closed ring structure similar to piperidine, was very useful since it is characterized toxicologically by a remarkable lack of toxicity and since pharmacologically it exerts a pronounced central sedative and hypnotic effect which develops rapidly and without an initial excitatory

stage. Quite in contrast to barbiturates it does not show a narcotic effect and produces in the EEG of healthy persons an activation of the alpha rhythm. With a dosage of 200 mg. given by mouth and with an average duration of action of 1½ hours it was possible to obtain positive activating effects in 72 out of 99 cases with epilepsy and in 24 out of 26 cases with cerebral tumours showing a normal resting electroencephalogram. A comparison was carried out with the effects obtained in epileptics after administration of N-Methyl-cyclohexenylmethylbarbiturates at a dose of 250 mg. given by mouth and with the investigations carried out under exactly the same conditions. Only 23 out of 99 cases showed a positive activating effect. In epilepsies an increase of the positive effects of activation with increasing feeling of fatigue was noted but this was not observed in patients with cerebral tumours. The testing of the administration of higher doses in epilepsies is discussed as well as the activity of Contergan as a useful activator in traumatisms, vascular processes and in other cerebral diseases.

25. Clinical and experimental EEG investigation in epileptics and healthy individuals with Preludin (2 - phenyl - 3 - methyl - tetrahydro - 1, 4 - oxacin - hydrochloride). — Bochnik and Spiegelberg, Hamburg.

This analeptic and fatigue inhibiting oxazine compound exerts, besides this effect a mild central circulatory influence. Transient increases in blood sugar concentration are only observed with intravenous administration. Clinically Preludin has been of use in cases with apathy without internal restlessness and as an active therapeutic agent in endogenous, reactive, psychopathic and organic cerebral diseases as well as in states of exhaustion (Spiegelberg). Preludin became better known as a drug able to inhibit the appetite. During the phase of recovery from disease, however, the stimulation by this drug also produces an increase in body weight. In its action Preludin has to be classified as somewhere between caffein and the amphetamines and this has been corroborated by physiological and psychological investigations. Magoun and co-workers observed in animal experimentations that Preludin produced a transient inhibition of cortical strychnine spikes.

In order to investigate whether this "ergotropic" drug administered in epileptics would be capable of improving their slowing and apathy without any danger of producing seizures, the drug was administered in 22 cases in large intravenous doses ranging from 50-300 mg. with simultaneous EEG control. In cases in whom there was a certain incidence of gross mental changes the tendency to seizure activity as measured by the EEG was not changed in 16 cases. In 3 cases there was improvement and in another 3 an impairment, one with occurrence of a generalized seizure. It is unknown to what extent in these instances incidental changes of activity may have played a role.

Diminution of a tendency for seizures precipitated by exhaustion by Preludin can be obtained since this drug acts against the fatigue. This is very remarkable from a therapeutic point of view.

In 3 narcolepsies, in 5 cerebral diseases of viral origin, in 5 general anaesthesias induced by Evipan as well as in an experimental alcoholic intoxication there was a disappearance of fatigue but no changes in the EEG attributable to Preludin.

In one psychopath and 3 epileptics 2 periods of abnormal behaviour without EEG changes were observed which developed on a background of vegetative affective decompensation due to the Preludin.

In a control group of 14 individuals without any cerebral disease there were despite a rather marked influence on the mental state no gross EEG changes. As in other groups fatigue was inhibited and the electroencephalogram sometimes became regular and beta-alpha activity was occasionally activated similar to what has been described by Colombati and Canerstrari.

In therapeutic oral doses of 25-50 mg. no activation of seizures was observed in epileptics. There is a certain caution to be exerted in psychopaths inclined to become drug addicts.

26. Concerning the problem of Cardiazol threshold. — Hans Keller, Munich.

The author reports first on the findings in 100 cases observed at the department of neurosurgery at Ischl and at the university neurological clinic of Munich, in whom fractionated Cardiazol and barbiturate activation measured in mg/kg. body weight were carried out. In patients showing previously a normal EEG and in cases in which pathological disturbances were suspected on clinical grounds or were clearly demonstrated, 26 normal EEGs were recorded, 21 border line tracings were obtained, and 53 abnormal records observed. An unspecific and a specific Cardiazol threshold was distinguished. Specific changes were most frequently seen in cerebral seizures and in tumours much more rarely in cerebral disturbances of traumatic or other origin and almost never in attacks of non-epileptic origin. The average values of the thresholds and the activation in convulsive disorders of various origins suggested a certain trend: the highest thresholds were found in psychogenic and non-epileptic convulsive disorders, relatively high values were found in post-traumatic epilepsy somewhat lower ones in symptomatic epilepsy, still lower values in epilepsies consecutive to cerebral damage having occurred in early childhood and the lowest thresholds in idiopathic epilepsy. Furthermore it was attempted to answer the question whether any conclusions could be drawn concerning the incidence of seizures from the measured level of the Cardiazol threshold. Surprisingly enough it was found that the highest Cardiazol threshold was found in cases showing an incidence of 2-4 seizures a month, whereas in patients having only one or two seizures every 6 months, and in those having very frequent seizures, 2 a week or even more, the threshold was found to be low. Since these data were obtained in a rather limited number of cases confirmation with re-studying of a larger group of patients is advisable.

27. Influence upon epileptogenic activities exerted by substances acting upon blood vessels. — J. Kugler, Munich.

The author carried out clinical and experimental investigations on the time course of EEG changes in epileptics occurring after injections of drugs known to be active on blood vessels.

Papaverin (0.05 g. in 10 cc. of isotonic saline injected over a period of 5 min.) and Hydergin (0.3/10 cc. over 5 min.) produced an activation as evidenced by increase in amplitude, decrease in frequency, number of pathological discharges, duration of paroxysmal discharges and increase of the delta index. The pulse frequency and blood pressure usually

decreased somewhat during this time. In contrast to this blockades of the stellate-ganglion on one side, with 10-20 cc. of Novocain at a dose of 10 cc. given intravenously over a period of 5 min. or at a dose of 20-50 cc. given subcutaneously and intramuscularly, betanicotinic acid derivatives (Ronicol, Dilatol) and Euphyllin (0.24/10 cc. over 5 min.) all produced, though with certain differences in the time course a diminution of the amplitude with increase of the frequency, diminution of focal discharges and shortening of the paroxysmal discharges. The validity of these findings was checked with control investigations when venous punctures for withdrawal of blood were carried out and in other controls where drugs of an entirely different type of action were injected.

Contradictions with the experimental, clinical and pharmacological findings of other authors were found.

The author discussed the following aspects of the problem:

(1) The complex activity of vaso-motor changes with subsequent metabolic reactions.

(2) In agreement with other authors the opinion is expressed that vascular spasms cannot be considered as primarily involved in the genesis of epileptic attacks.

28. The use of Pyrifer as an activation method. — H. E. Kehrer, Jun., Münster.

It was attempted to activate the electrical activity of the cerebral cortex in epilepsies and other cerebral diseases by Pyrifer hyperthermia. The procedures consisted in giving to patients which previously showed a negative or uncharacteristic EEG an injection of 50 units of Pyrifer (strength 1). About 24 hours later an EEG was recorded.

With this method of provocation, more or less pronounced dysrhythmic disturbances, diminished frequencies and increased amplitude of discharges were obtained in 9 epileptics. These changes increased under hyperventilation. Clear focal changes when previously only generalized disturbances or normal activity were present were observed in 5 cases. The localization of these electroencephalographic foci were almost all lateralized on the same side on which the pneumoencephalogram had indicated the location of the lesion. In 6 patients without cerebral disease such pathological EEG changes after Pyrifer activation were not found. This type of activation was not successful in 3 epileptics, 2 of which had cortical and one questionable psycho-motor attacks. In other patients without attacks, in whom the pneumo-encephalogram showed some residual cerebral damage this type of activation produced a mild generalized dysrhythmia without focal signs, but with absent alpha activity.

The activation of the EEG does not occur at the peak of the fever but after the decline of the hyperthermia, i.e. in the period of counter regulation.

It is known that due to the increase of the blood globulins in inflammatory diseases the tendency to seizures in epileptics is diminished. Frisch, however, found that after a bout of fever there is always a counter reaction with a period of increased frequency and increased severity of attacks.

Pyrifer injection is well suited for the EEG activation, because it exerts a stimulating effect upon almost all central regulatory mechanisms and because the effective counter-regulation following its administration is a physiological process which is most likely related to the processes which precipitate the spontaneous attacks in epileptics.

29. Photic stimulation. — Schaper.

The author reports on its experience with photic stimulation in 2000 children and adults. The cortical responses upon illumination of the retina are classified into non-paroxysmal and paroxysmal reactions.

The most important non-paroxysmal reaction is the simple harmonic synchronization characterized by the 1:1 relationship between frequency of the photic flashes and occipital responses. This response is discussed in detail and its dependence upon age pointed out. Short reference is made to the sub-harmonic and multiple harmonic responses, as well as to the criteria of the pathologically significant asymmetries of the response.

The paroxysmal reactions are divided into 3 groups : (1) photic sensitivity, (2) photo-convulsive response, (3) photo-myoclonic response. In the latter according to clinical and electroencephalographic criteria 4 sub-groups can be observed. Findings: in 375 children and adults without convulsive disorders and without neuropsychiatric symptoms, paroxysmal reactions were activated in 3 per cent. In convulsive patients the number of findings of diagnostic significance after normal breathing and hyperventilation were increased by 10-25 per cent.

In neuropsychiatric syndromes and psychosomatic diseases such as in neurosis, vomiting, fainting, headaches, umbilical colics, pubertary anorexia, asthma and others, paroxysmal reactions were activated in 15-30 per cent of the cases.

30. Photic stimulation. — Leischner.

The author points out that of the pharmacological activation methods in EEG practice have only a relative value. The results of photic stimulation in 100 patients with organic brain damage from the ''Rheinische Landesklinik für Hirnverletzte'' in Bonn are reported. In all these patients the resting EEG was first recorded then the EEG during a 5 min. period of hyperventilation and after this photic stimulation for 5-10 min. was carried out with the ''Strobotest'' apparatus of Schwarzer. First single flashes of a frequency of 2-30 c/sec. with a constant change in frequency were applied. Hereafter twin flashes were presented with intervals between the single flashes varying between 30-170 msec. The twin flashes were separated by intervals of 25-500 msec.

In the 100 patients investigated 36 cases showed additional changes in the EEG when compared with the record taken at the resting state and during hyperventilation. However, in only 22 instances these changes were of a pathologically significant character. Most of these changes consisted of waves in the theta frequency band or rarely in the delta frequency band. Only in a few cases convulsive potentials or focal dysrhythmias were encountered. Only in 4 patients photic stimulation alone was able to demonstrate a pathological EEG change. In 18 cases there was merely an accentuation of a previously detected pathological finding. Localized disturbances were encountered in 13 cases. It appeared that twin flashes were more potent than single flashes.

31. Prodromal symptoms as an activating factor for the EEG in epilepsy. — K. Pateisky.

In a certain number of epileptic patients the EEG at rest and during hyperventilation and with the usual activation procedures remains normal. A detailed study of the history, however, shows that such

patients often complain of disturbances between their attacks and especially in the prodromal phase and during the aura which can be explained by the mechanism which Potzl described as ''Erregungsfang'' [= capturing of excitation]. Such patients often give the history, that they suffer from periods of obsessional repeated memories often with a content describing the situation in which the first attack occurred or related to the original trauma which caused the epilepsy. The relatives of such patients often notice periods in which the patients show nervous tension without any apparent cause and vegetative disturbances which often are followed by an attack. These patients were asked to come for an EEG examination at a time when they experienced these prodromal signs. In the majority of cases the EEG was found to be abnormal during this period. It is therefore possible to carry out EEG examinations in these patients at a period which is most opportune moment for finding abnormalities and this procedure can be equated to the efficiency of the activating procedure.

32. The EEG in poriomanics. — Wissfeld, Frankfurt/Main.

The electroencephalograms in 50 poriomanics were normal in 26 and abnormal in 24 cases. Besides generalized disturbances with dysrhythmias and slowing of the rhythms, localized focal changes were found in 2 cases and in 10 cases epileptiform disturbances were brought out by hyperventilation. The majority of poriomanics are represented by epileptoid psychopaths (16) and patients with organic brain damage (11). More rarely one finds oligophrenia (7), neurotic conflicts (7), environmental factors (6) and unsteadiness of character (3) as the cause for the poriomanic urge to run away. Most of the EEG changes are seen in epileptoid psychopaths and in the patients suffering from organic brain damage, whereas the other groups usually showed a normal EEG. On the basis of the clinical and electroencephalographic findings one can assume that about half of the poriomanics show evidence for cerebral pathology. On the other hand there are tansitory conditions between an organically determined cause to those which are of a purely psychological nature.

33. Latent epilepsy in the EEG of children and adolescents presenting behavior problems. — Eiden, Munich.

More than 50 per cent of abnormal EEGs were obtained in 500 children and adolescents which were psychologically abnormal and presented a behavior problem. In none of these there was any indication for a convulsive disorder from their history. Quite frequently EEG signs of residual epilepsy (about 50 per cent of the cases) were found and in 2/3 of the cases these involved the left hemisphere with signs of focal convulsive discharges which were mostly found in the temporal region. ''Latent epilepsy'' was found with clearly defined convulsive potentials mostly of the type encountered in temporal lobe epilepsy. Borderline findings described as ''increased excitability of the central nervous system'' manifested themselves in the form of bursts and synchronized discharges occasionally of a paroxysmal character with steep 3-6 c/sec. slow waves and some sharp waves which, however, did not assume the form of typical epileptiform potentials.

Besides hyperventilation a good activation procedure in children was to take the record in the fasting state. Thus quite frequently epileptogenic potentials became more prominent and the EEG diagnosis could be confirmed.

Follow-up studies with EEG control records in these psychologically abnormal children and adolescents showing abnormal EEGs are considered as necessary in order to arrive at a more clearly defined concept of the electroencephalographic (not clinical) concept of ''latent epilepsy''.

34. Unexpected epileptogenic findings in several conditions with disturbed mood. — Bochnik, Hamburg.

Irritable, depressive and maniform changes of mood without any alteration of consciousness as seen in some epileptics were considered by the classical psychiatry, on the basis of genetic and symptomatological arguments, as due to combination of epilepsy with cyclothymia, schizophrenia or psychopathic personality changes. EEG investigations in relatives of epileptics, psychopaths, migraine patients and in children with behavior disturbances, umbilical colics, etc., showed that epileptogenic disturbances are often encountered besides more common functional changes of a different character. The author reports on the relationships between changes in mood and electrographic disturbances in the EEG which are not well known and which are demonstrated with a few clinical examples. The clinical picture in these patients often show atypical symptoms and complex changes. The frequent diagnostic question, whether this is a case of epilepsy or not, when paroxysmal changes are recorded in the electroencephalogram, is an unfruitful approach to the problem. It is more important to evaluate the importance of the electrographic disturbance in relation to the single case to be studied. Such electrographic disturbances can be very relevant or only indicate the presence of an additional modifying factor, or it can be without any importance at all. The cerebral disturbances underlying these electrographic changes may determine or favor mental disturbances such as lack of inhibition, irritability, coarseness of character, changes of affectivity and of mental and motor speed, as well as vegetative changes and their paroxysmal manifestations. These changes can be associated with clinical syndromes not necessarily of an epileptogenic nature. The establishment of an abnormal EEG is also valuable as an ancillary finding since the institution of anti-convulsive therapy is sometimes helpful in the cases in view of the possibility to interrupt a vicious circle. Furthermore, the electroencephalogram is helpful in ambiguous syndromes where it is important to distinguish between primarily organic or primarily psychogenic disturbances. The pathological EEG changes in the form of diffuse changes, focal disturbances, paroxysmal dysrhythmias and convulsive discharges are encountered in certain patients with very markedly abnormal personality and in paroxysmal and exogenous disturbances in patients suffering from endogenous psychosis. Etiologically, these disturbances are often related to early childhood cerebral traumas and to hereditary forms of dysrhythmia.

Special mention was made by the author of patients with long standing depressive syndromes and marked epileptogenic EEG changes without any clear history of epileptic attacks. These patients are sometimes improved with anticonvulsive medication.

35. EEG in febrile convulsions. — SCHAPER.

Investigations in children with febrile convulsions show that one out of 3 children later developed convulsions even without fever. In patients who were free of seizures for ten years, 40 per cent showed epileptogenic potentials in response to photic stimulation and therefore had to be considered as still potentially epileptic. From a practical point of view the conclusion is warranted that prognosis in febrile convulsions is rather serious. It is indicated to prescribe anti-convulsive medication for a long period of time after the first febrile convulsion and to prescribe an anti-pyretic drug as well, which the patient is ordered to take as soon as the first signs of intercurrent infections manifest themselves.

36. Electroencephalographic and clinical observations concerning the therapeutic effect of Diamox (Azetazolamid) in epilepsy and in conditions with increased intra-cranial pressure. — K. PATEISKY and H. PETSCHE, Vienna.

Diamox is a potent inhibitor of carboanhydrase and produces alkalinization of the urine, slight acidosis of the blood, increase in CO_2 content of the tissues and excretion of water retained in oedemas. Diamox was first used as a dehydrating drug in order to arrive at a better localizing diagnosis in focal cerebral lesions attended by marked increase of intracranial pressure. Pathological changes in the EEG, however, showed improvement under Diamox, even when no oedema was responsible for the initial pathological changes in the electroencephalogram. With Diamox the duration and number of the paroxysmal discharges (paroxysmal delta, spike and wave complexes of any form, paroxysmal dysrhythmias) diminishes and dysrhythmic EEG patterns become more normal. There is an increase in the amplitude and the regularity of the alpha rhythm. The activity of the focus itself is not influenced, but focal changes become more apparent because of the diminution of the diffuse disturbances. On the basis of these experiences Diamox was given a therapeutic trial in cases of epileptic status and in conditions associated with raised intracranial pressure (52 patients). In epilepsies the therapeutic effect was best, as could be expected, when generalized paroxysmal changes were present. In epileptic status and in conditions associated with increased intracranial pressure Diamox was especially helpful since it exerts a two-fold effect, first dehydrating the tissues and secondly diminishing the excitability.

37. Electroencephalographic studies concerning the action of LSD 25. — D. BENTE, T. ITIL and E. E. SCHMID.

In view of the fact that pharmaco-psychiatric forms of treatment as well as the classical treatment with insulin coma and electro-schock result in the slowing of the spontaneous cerebral rhythms, the effect of the hallucinogenic drug Lysergic acid diathylamid (LSD 25 "Sandoz") upon syndromes characterized by slowing in the electroencephalogram was studied. The drug was given at a dose of 20-150 gamma.

Pre medication with LSD 25 inhibits the development of slow waves under the influence of Evipan and Pentothal. Slowing of cerebral rhythms due to chlorpromazine is also inhibited by LSD pre medication. In akinetic-abulic syndromes produced by combined Reserpin-chlorpromazine medication and associated with slowing of the background rhythms in the EEG as well as in similar EEG pictures due to repeated electro-shock treatments, LSD 25 produces an increase in acceleration of the cerebral rhythms with concomitant reduction of the amplitude and finally induces periods of flat activity with beta rhythms.

An impressive effect of LSD 25 lasting for several hours can also be observed in severe general disturbances encountered in epileptic patients. Here also there is a progressive accelleration and diminution of amplitude of the brain rhythms. Initially there is often an appearance of synchronized rapid rhythms occurring in bursts. Clinically, one observes in these cases often a transient sleepiness. When paroxysmal slow waves are present LSD 25 inhibits the slow components and produces an increase in spike activity and therefore can precipitate an attack. LSD 25 therefore not only influences psychical function, but also exerts a marked effect upon cortical electrical activity. In view of the antagonistic effect produced by LSD to that produced by the new neuroleptic drugs interesting approaches to pharmaco-psychiatric problems can be developed.

38. Clinical diagnosis and the incidence of positive clinical findings in electroencephalograms showing pathological changes. — BEHREND, Hamburg.

The problem of correlation of EEG changes with neurological syndromes has been often discussed. Divergent views which have often been expressed are partly due to the diversity of the patient material studied in psychiatric neurological and neurosurgical clinics. In the period from the 1st of January 1951 to October 31st, 1955, 7449 EEGs were taken at our clinic on a total number of 6111 patients; 4592 final diagnoses were made. The material on which these figures were obtained consisted of out-patients and neurological and neurosurgical in-patients. These figures concerning the incidence of positive diagnosis in abnormal EEGs in a patient material including a multitude of different clinical diagnoses may appear surprising. They are, however, in accord with what a clinician expects from the EEG. The purpose of this study was to express this subjective experience in quantitative terms.

PRINTED IN CANADA

SOCIÉTÉ D'EEG ET DES SCIENCES CONNEXES DE LANGUE FRANÇAISE

Paris, December 5th and 6th, 1956

Secretary: M. B. DELL

9, rue Jasmin, Paris XVIème, France

1. Electromyographic investigations of the electrically stimulated healthy and pathological muscle in man. — R. HUMBERT, A. DEHOUVE and P. LAGET, Paris.

The authors first describe the principles of a method of stimulation with remote control allowing to excite in man a normal and pathologic muscle through the skin and to record simultaneously its electromyographic response without any appreciable distortion by the stimulation artifact regardless of the duration of the stimulation.

The square wave pulse used as the stimulus is perfectly well defined in duration and voltage and reaches the preparation directly and not by the intermediary of a train of high frequency waves. It allows the use of long time constant amplifier. In this report the authors expose the results in a certain number of normal and pathological cases, obtained with the aid of this method. Observations in adults and children are reported.

The records obtained with this type of electromyography are presented for muscles showing partial or total degeneration and an analysis is given of the different aspects which the evoked fibrillation can assume. Its relationship with the ''macroscopical'' slow contraction and with the galvanotonus is outlined. The systematic study of the provoked electromyogram by stimulation of the healthy muscle shows that there is an extreme variety of responses which can be thus obtained: direct, reflex or mixed.

This variability is obtained regardless whether stimulation was applied to the nerve trunk or to the motor point or outside the motor point. These observations lead to the study of the relationships which may exist between electromyographic responses and chronaximetry such as it is practiced in classical electro-diagnostic methods.

2. Electrophysiological study of a trigimenal monosynaptic reflex. — A. HUGELIN and M. BONVALLET, Paris.

A brief electrical shock applied intracranially on the afferent branch (mesencephalic root of the 5th nerve) of Szentagothai's trigeminal two neuron arc, evokes a reflex discharge routinely, which may be recorded on the masseter nerve.

The temporal course of the reflex potential and the conduction velocities measured on the different elements of the circuit show the existence of a complete homology between the functional characteristics of the afferent and efferent fibers of the trigeminal reflex, and those of the proprioceptive and motor fibers of the spinal myotatic reflex. The nuclear delay of about 1 msec. (minimum 0.85 msec.) which has been calculated seems to indicate that only one synapse is involved in the transmission of the response.

The classical electrophysiological demonstration of a monosynaptic link is given by the sudden appearance of a direct motoneurone discharge, without any shift of the reflex response, when the spread of current due to a stronger stimulus excites directly the motor nucleus.

On the other hand, it has been observed that impulses from the supratrigeminal nucleus are electively able to inhibit the masseterian motoneurones. This observation together with histological data demonstrate the existence of an anatomically distinct structure responsible for inhibitory influences on the jaw closing myotatic circuit.

The interest of the above preparation will be to permit investigations on the effects of cortical and subcortical influences on the excitability of motoneurones in the ''encéphale isolé'', that is to say by preventing the disturbing effects of anesthesia and sympathetic variations of reticular origin.

3. A study of the cuff test under electromyographic control in latent tetany of the adult. — F. THIÉBAUT, C. ISCH-TREUSSARD, J. EBTINGER-JOUFFROY and F. MAZOUE, Strasbourg.

In 150 patients above the age of 16 in which latent tetany was suspected, the cuff test under electromyographic control was practised. The activity was recorded in the first dorsal interosseous muscle. The ischemia was maintained during 10 min. by applying a blood pressure cuff to the arm. No concomitant hyperventilation was carried out. During the time of ischemia activity was noted in only 27 cases. After removal of the cuff, repetitive activity with at least 5 discharges appeared in 73 cases. From the clinical point of view, it is important to note that there is a high incidence of positive tests in patients suffering from anxiety. The incidence of positive tests is definitely lower in those patients who complain about parethesias and visceral sensations. There was no parallelism between a positive Chvostek sign and abnormalities in the electromyogram. The most interesting correlations are shown by the changes in clinical and electromyographic signs induced by treatment with calcium and A. T. 10, which was supplemented in refractory cases by the administration of Vitamin D and parathyroid extracts. In 45 patients which showed a positive test follow-up studies before and after treatment could be carried out. In all these cases there was a striking parallelism between the clinical evolution and the abnormality in the EMG. Clinical recovery was associated with disappearance of the EMG abnormalities and clinical improvement with attenuation of the EMG signs. In cases which did not respond to treatment, or where the treatment was insufficient, there was persistence of the EMG disturbances.

4. Myographic analysis of electrical neural activities. — P. DELMAS-MARSALET, Bordeaux.

The classical procedures of the analysis of the EEG attribute to the underlying components the form

of regular sinusoidal waves. The mathematical addition of the sinusoidal forms according to the laws of Fourier does however not consider the refractory periods of nerve cells.

The author's studies on human striated muscle showed that the refractory period of this muscle appeared to be equal to that of nerve cells. Furthermore, the mechanical response of the striated muscle to a faradic excitation of brief duration assumed a form which was very similar to that of an action current of a nerve cell. It therefore seemed that the combination in the same muscle of mechanical activities resulting from excitation by several faradic circuits, the frequencies of which could be regulated and combined at will, would produce a resultant curve more conform with the summated activity seen in the EEG than that obtained on the basis of summation of sinusoidal components, a method which ignores the existence of refractory periods.

The study of the mechanical results of such additions of known frequency components, and their comparison with identical forms seen in the EEG, could thus allow to know the frequencies which are the real components making up the morphological forms in the EEG. This is the principle which the authors call ''myographic analysis of complex neural activities''.

The technique used by the author is very simple and consists in stimulating the human biceps muscle by two, three or four different trains of non-tetanising and sub-maximal faradic stimulations, at frequencies which can be regulated by the tyratron of each individual faradic apparatus. Each different faradic circuit ends in a large common electrode applied to the biceps muscle. The contractions of the muscle are recorded with the aid of a Marey myograph on a Marey drum. Gas filled tubes isolate the faradic circuits from each other. The results show that where more than twenty sinusoidal components were necessary to produce a spike and wave complex by their additive summation, two components (acting upon the muscular receptors having a refractory period), were sufficient to reproduce this form by combination of frequencies which were always the same. Two components, the frequencies of which were modified, allowed to obtain all types of spindles seen in the electroencephalogram. With three components, it was possible to reproduce all the forms seen in the epileptic encephalogram. Fragments of the EEG, representing activities of 10-13 sec., could be rigorously reproduced by combining frequencies and amplitudes of the muscular responses to excitation of the two or three faradic circuits. Illustrated samples of tracings were shown to underline the importance of these observations.

Conclusions:

1. This method of myographic analysis of complex electrical neural activities, allows to reproduce all the forms of spindles seen in the normal EEG and to define their elementary components. It shows how the ''perfect spindle'' which is only realized for very small shifts of the frequency of each component, is in fact a mechanism which reduces as much as possible the addition of cerebral electrical activities to high potentials which could become harmful to the brain.

2. From a combination of frequencies giving perfect spindles, one can by progressively modifying one of the components, see how all forms of ''degraded'' spindles can be produced which finally lead to the isolated spike.

3. All of the abnormal forms of the epileptic EEG could be easily reproduced with two components only, or with three at the maximum (bursts of slow waves in a tracing with rapid waves, spike and wave complexes, sinusoidal waves, multiple spike and waves complexes).

4. In cases where two components result in the formation of spindles comparable to those seen in the occipital electroencephalogram of a normal subject, the production of a third component at a frequency of 4, 5, 6, 10 or 15 c/sec. produced disturbances of the spindles in the same way as those seen in the occipital electroencephalogram when intermittent photic stimulation with these frequencies is used.

The author feels that the sum total of the observed facts cannot be explained on the basis of a mere analogy. This method is in fact an indirect analysis of complex electrical activities of the nervous system.

5. An experimental study of certain convulsive drugs: their relationship of the excitability of the reticular system. — R. NAQUET, G. DROSSOPOULO and G. SALAMON, Marseille.

The authors report on a study of the effects of slow intra-venous injection of two convulsive drugs, Megimide and Cardiazol, in non-anaesthetised cats immobilized with Flaxedyl in which the spontaneous electrical activity of the cortex and evoked potentials were recorded.

Both these drugs produced a slow synchronization of the activity but is was not possible with these experimental procedures to differentiate in a qualitative way the effects of Megimide and of Cardiazol. Cardiazol of 2.5 per cent was used, the same as Megimide (5 mm. per cc.) The action of Megimide upon evoked potentials is similar to that of Cardiazol and modifies their form and distribution on the cortical surface as well as in reticular structures. It favors, as Cardiazol does, the appearance of epileptiform afterdischarge. The different activities evoked by these convulsive drugs can be influenced by direct or indirect stimulation of the reticular system. The authors describe two stages: the first, appearing with moderate dosage, where the modification induced by these convulsive drugs consisting of slow synchronization, modification of the form and distribution of evoked potentials becomes reversible simultaneously with the appearance of desynchronization of the record. With higher dosage, which produces a pre-convulsive stage, the reticular stimulation is no longer capable to desynchronize the record and has no or little effect upon the evoked potential. It may, however, precipitate a generalized seizure.

6. Modifications of the electrical activity of the rhinencephalon. Behavioral changes induced by hypophyseal gonadotrophic hormones in the female rabbit. — J. FAURE, Bordeaux.

Awake, freely moving animals with implanted electrodes held in place by a plate were studied with polygraphic methods. The activities of the different parts of the rhinencephalon, especially of the Ammon's horn and the corticomesial part of the amygdala, were recorded simultaneously with that of the ventromedial hypothalamus. Subliminal electrical stimulations were carried out before the administration of these hormones in certain animals, whereas in others

only hormones were given. Histological verification of electrode positions were carried out when sacrificing the animals several months later. It was found that the gonadotrophic hormones can produce the same behavior, the same vegetative variations and the same electrical changes as certain subliminal electrical stimulations. Histamine and acetylcholine favor these effects.

Furthermore, the action of electrical stimulation was facilitated by the presence of gonadotrophic hormone. A typical olfacto-genito-sexual behavior appeared. During its course, changes in activity appeared in recordings from the amygdala, Ammon's formation and the ventromedial hypothalamus. This olfacto-genito-sexual behavior and its variations could be reproduced by ocytocine. Therefore, a rhinencephalic participation in the process of regulation of diencephalo-hypophyseal mechanisms is suggested.

7. The electroencephalogram during experimental attacks of asthma in guinea pigs: electro-anatomical confrontations. — J. Faure, J. Gruner, R. Quilichini and J. Gueyne, Bordeaux.

A polygraphic study was carried out in 10 freely moving awake guinea pigs which were placed in a glass cage, into which an aerosol of histamine was introduced. Death occurred after variable delays, but always fairly rapidly. The electroencephalogram and corticogram showed rhythmical discharges at 4-5 c/sec. of a short duration followed by rapid activity of low voltage and finally extinction. Respiratory and electrocardiographic changes were correlated with these variations. In subcortical structures the same variations were found, but in the hippocampal formation and the lateral thalamus the most spectacular changes were observed and there was an earlier extinction. On the other hand, use of a protecting drug showed that the amygdala, the hippocampal formation and the lateral thalamus were selectively involved. Anatomical studies of control brains suggest that the disturbances due to histamine associated with bronchial spasms, consist of very particular disorders: vasodilatations, generalized hemorrhages of the brain which are most pronounced in the hippocampal formation, the lateral thalamus, the basal ganglia, the brain stem and the cerebellum. Only Ammon's horn, the lateral thalamus, the cerebellum and the temporal cortex showed edema when the attack was brief. There was, therefore, a close correspondence between the anatomical lesions and the bioelectrical disturbances.

8. Cortical sensory responses in the cat (chronic preparation). Their modification during the establishment of temporary connections. — P. Buser and A. Rougeul, Paris.

This study was carried out in animals with implanted bipolar electrodes located in different cortical regions, particularly in the projection areas. The animals were exposed to different modalities of sensory stimuli (tactiles, auditory, visual), which were simple or combined. The evoked cortical responses were observed, with the method of superposition on a cathode oscillograph.

As was previously seen in non-anaesthetised preparations (Buser and Borenstein) one can observe sensory responses of a "secondary" character (polyphasiques and of long latency) in chronic animals. These responses are found outside the primary projection areas selected to the modality and site of the applied stimulus. These secondary responses showed greater variability than the primary evoked potentials. In the normal animal this variability can be correlated with certain psychological situations, among them that of conditioning.

1. An intense and unexpected stimulus, provoking a orientation reaction and "activating" the cortical electrogram produces an abolition of these responses (external inhibition).

2. When the attention of the animal is oriented to stimuli of a certain sensory modality, the record taken from the primary sensory area of this particular modality can show a transient appearance of a "secondary" response, evoked by a different modality, or, if such a "secondary" response was already existing, it may become enhanced.

3. Finally, when a conditioning stimulus is regularly combined with a different second stimulus of an unconditioned character, one observes a typical increase of the "secondary" response recorded in the primary area of the second stimulus when the first stimulus is applied. This particular reactivity of the "unconditioned area" to the signal stimulus seems to be a characteristic of the establishment of a temporary connection with what was already observed by other investigators. (Morell and Jasper 1956; and Jouvet and Hernández-Peón 1955).

The authors think that nevertheless this may represent a type of facilitation of cortical projections, which may occur also in other situations than conditioning.

9. The cortical auditory response in man studied by an integration method. — J. Calvet, H. P. Cathala, J. Hirsch, J. Scherrer and F. Contamin, Paris.

The detection in the scalp electrogram of potentials evoked by a brief auditory stimulus was rendered possible by a method of integration which consists in transforming the electrocortical phenomena into variations of the luminosity of the sweep of a cathode ray oscillograph. The photographic record of 100 or 150 successive sweeps triggered by the stimulation forms the basis of the integration. The reading of these records with a photoelectric cell produces a tracing of the customary aspect.

The evoked auditory potential appeared in the form of a complex disturbance. After the latency of 15 to 30 msec. one is able to distinguish a first grouping of phenomena consisting of a polyphasic and rapid potential variation of a duration of 30 to 40 msec. This is followed by oscillations which are rapidly damped. It is interesting to compare this auditory response with the one recorded in animals, and also with the response recorded in man by somatic and visual stimulation, studied by the same methods of integration as is used here.

10. The microvibrations of the body as an expression of physiological tonus. — A. Denier, La-Tour-du-Pin.

For two years the author has studied a new technique based on the work of Rohracher, reported at the Symposium on Vegative Neurology, held in Vienna on the 30 July, 1954.

The detection of the microvibrations is made possible by a pickup device using sodium-potassium-tartrate crystals glued on the muscles of the different regions intended to study. The changes are amplified and recorded with a magnetic oscillograph activating a pen writing device.

In normal man the microvibration had a frequency of 6-12 c/sec. with an amplitude of 1 to 5 micra during relaxation. The tension of the muscles produced an augmentation of the amplitude to ten times as great, without any change in frequency. During sleep, the amplitude was reduced to half of its initial value, and under anesthesia to a third of its initial value. During hyperthermia and in hyperthyroidism the frequency was augmented to 14 c/sec.

Only homeothermic organisms present these microvibrations. In guinea pigs, dogs, rabbits and mice, under hypothemia the amplitude is reduced and there are intervals with silence.

In poikilothermic animals such as the toad, the frog, and the turtle, these vibrations could not be recorded.

The absence of these microvibrations in poikilothermic animals and in hibernating animals, the augmentation of these vibrations by fever and hyperthyroidism in homeothermic organisms, show that they are in relation with the physiological tonus and the cutaneous temperature, dependant upon impulses delivered by the autonomic nervous system.

The recording of these microvibrations allows to recognize modification in the local physiology of the muscle, or the presence of central disturbances which affect different regions of the body.

With this method modifications can be studied which are produced by different diseases such as parkinsonism, multiple-sclerosis, amyotrophic lateral sclerosis, poliomyelitis, Aran Duchenne's disease, causalgia, tropho-neuritic disturbances, Sudek and Leriche's disease, etc.

This technique can be used as a complementary method to that of determining the chronaxy of electromyography and electroencephalography.

11. Technique and method of recording of ocular movements in neurology: applications of the method to the study of reading. — A. Rémond and V. Gabersek, Paris.

The use of oculography in Neurology led the authors to design an electrographic method of recording of eye movements. Thus the problems raised by the study of eye movements may be adequately investigated. These problems belong to the field of neuro-ophthalmology and also deal with the study of the more subtle modifications of the specific characteristics of ocular movements during reading as seen in different neuro-psychiatric conditions.

The authors use the ordinary electrodes employed in electroencephalography. These are fixed upon special goggles which have already been described earlier. Eight electrode positions are usually recorded from, among which five at least allow analysis of the movements of the eyes and three others give the electroencephalographic and electrodermographic background. The record is amplified either by an AC or DC amplification system. The subjects are seated in front of a table at a constant and precise distance from a reading stand which is uniformly lighted.

The standard examination comprises the following different stages:

(1) The record of the spontaneous movements at rest with eyes opened and then with eyes closed (2 min. strip of record for each).

(2) Recording of the eye movements under command with movement of gaze into the four cardinal directions, again with eyes opened and eyes closed.

(3) Recording of the eye movements during the visual inspection of a geometric design and of colored plate (diagnosis of dyschromatopsias) or of a plate with fragments of a text (diagnosis of dyslexia).

The tracings are analyzed from two different points of view. On the one hand, vertical deflections of the record are analyzed which correspond to eye movements and on the other hand, the time periods which separate these deflections and which correspond to the periods of arrest of eye movements.

12. The displacements of the gaze during reading: I. The eye movements. — A. Rémond, V. Gabersek and N. Lesèvre, Paris.

Electro-oculographic records have been used for a long time in attempts to demonstrate abnormal eye movements, particularly in the study of nystagmus. This matter has been applied much less to the study of normal movements, for instance those occuring during reading. These latter were of interest to neurologists, but were particularly studied by psychologists using photographic and cinematographic techniques.

With the aid of a standard electrographic technique described elsewhere, the authors were able to distinguish during reading four types of eye movements:

1. Return movements to the line: L
2. Rectifying movements: R
3. Movements of progression: P
4. Movements of verification: V

Only the movements of progression are directed from the left to the right (in reading occidental languages) whereas the other types of movements are directed from the right to the left.

The authors demonstrate for these different types of movements a proportional relationship between the amplitude of the deflections corresponding to the movements, and the angular excursions of the movements of gaze.

A comparative study of the frequency of occurrence of the different types of movements was made and this allowed to distinguish for each type a characteristic variation. The mean amplitude of the movements of each variety was studied in detail. The frequencies of occurrence and the amplitudes are compared and presented in detail for each normal individual.

13. The displacements of gaze during reading: II. The periods of arrest of gaze. — A. Rémond, V. Gabersek and N. Lesèvre, Paris.

Using a technique described elsewhere, the authors recognized the usefulness to carry on an analytic study of the time periods separating the different types of eye movements during reading. The authors distinguish about ten different types of arrest of eye movements according to which type of movement precedes and which type of movement follows each of these arrests. The proportional relationships of these types of movements were also studied. The duration of these arrests was studied with statistical methods and the difference of duration of each type underlines the usefulness to differentiate them from each other.

The simultaneous study of movements and arrests led to consideration of the nature of the positions of gaze during each period of arrest, the function of the visually analyzed object or of the text being read.

A graphic representation of the findings, called "Scopogram" gives a useful summary representation

for each analyzed individual and each analyzed text. It allows to appreciate the different findings concerning the number and amplitude of the movements, as well as the duration of the periods of arrest and the position of the eyes during these periods.

14. Efficiency of reading in normal subjects. — A. RÉMOND, N. LESÈVRE and V. GABERSEK, Paris.

The findings which were obtained in studying the displacements of gaze during reading by distinguishing the nature of the movements and their amplitude, the duration of arrests of movement and the position of the eyes during arrests, were regrouped in a statistical study of a population comprising about 100 individuals.

It was then possible to recognize the amount of statistical dispersion for each of the variables and to attempt to interpret them as the function of the nature, the complexity and difficulty of the text, the length of the lines, the number of words or signs per line, the type of character of the print and the meaning of the text.

The importance of the state of attention, of training and of cultural level and age appeared very clearly in this study.

15. Electrodermogram recorded simultaneously with the EEG. — J. VAN BORK and A. RÉMOND, Paris.

In 200 patients having an electroencephalographic examination the authors studied the frequency of occurence and the importance of electrodermographic changes of spontaneous onset which could not in any evident way be considered as psychogalvanic reflexes. These patients were chosen at random and were not submitted to any preparatory measures.

The degree of this dermographic activity could be used to evaluate the effect of the "recording situation" upon different individuals and could be compared with the electroencephalographic pattern.

Only the "Targanoff effect" was recorded on the routine electroencephalographic apparatus in parallel with the EEG. The aspects particularly studied were the amplitude of the crest of the first negative deflection and its time course.

The following findings were obtained: a progressive diminution though rather slight of the number of electrodermographic changes with age. There is also a diminution of the amplitude of the electroencephalographic changes with age. The absence of electrodermographic changes of apparently spontaneous onset is much more frequently encountered in cases where the electroencephalogram shows signs of organic cerebral pathology. In the normal electroencephalogram the electrodermographic changes are absent especially in individuals under treatment with chlorpromazine or barbiturates.

There was a significant correlation between a large amplitude electrodermogram and a marked lability of the electroencephalogram.

16. Temporal and spatial integration using the same apparatus. — A. RÉMOND, Paris.

The apparatus for topographical analysis used for several years at the "Salpêtrière" was re-designed in order to allow the use of the same apparatus as a topographical analyser and a topographical integrator. To this effect several changes were carried out and especially the time base was re-designed. The switching over of the apparatus from one use to the other can be carried out with a single switch.

(1) A topographical analyser writes successively, at a frequency which can reach as high as 1500/sec., the contours of the potentials of a special electrode assembly.

(2) A topographical integrator allows to isolate out of its spontaneous activity the contour of an instantaneously evoked potential recorded in a sensory structure at a fixed time after an applied stimulus which may have been presented up to several thousand times.

(3) A time integrator isolating out of the spontaneous activity of a sensory region the variations in time characterising a response evoked by an appropriate stimulus.

17. The electroencephalogram in menstrual disturbances. — J. FAURE and P. LOISEAU, Bordeaux.

The correlation of the electroencephalographic pattern, the hormonal balance and the clinical history of women suffering from menstrual disturbances was studied by the authors.

A series of 40 subjects with a complete endocrine work-up was studied. This study is an addition to a previous series of around 250 patients which has already been reported.

The methods used were the same but completed by an instrumental analysis. In this series the types of electroencephalographic patterns which were recognised previously and divided into five groups on the basis of electrical and hormonal changes were again encountered. This therefore confirms that it is the hormonal imbalance, rather than the clinical syndrome which is correlated with the particular EEG characteristics. The study of the syndromes shows that the hypophysio-ovarian imbalance, hypothalamic amenorrhea, menopausal disturbances, certain types of hormonally determined obesity and adreno-cortical reactions are the conditions which most often produce EEG changes in the series here presented.

18. Contribution of the electroencephalogram to the diagnosis of lesions of the posterior fossa. Review of 131 verified cases. — R. GONSETTE, G. ANDRE-BALISAUX and J. COLLE, Louvain.

In this study the patients were grouped according to the localization of the lesion. The EEG was analysed in 25 tumors of the cerebellar-pontine angle, 32 tumors of the cerebellar hemispheres, 11 abcesses and hematomas, 20 tumors of the midline (vermis and 4th ventricle), 30 tumors of the bulb or pons and 13 cases of intracranial hypertension without a neoplastic lesion. The authors describe in these different cases changes of the EEG, whose particular morphology and sensibility to functional activation procedures, helped to establish the clinical diagnosis. The records were abnormal in 74 per cent of the cases.

On the beginning of the disease process one notes a slowing and instability of the background rhythm. Later localized theta activity in temporal and posterior regions is observed. This activity reacts only little to opening of the eyes, but is amplified by hyperventilation. The disturbance is never localized, except when the pathological process invades the middle fossa. In a more advanced stage, delta waves of an occipital or frontal localization appears, intermingled with an altered background rhythm. This delta activity is reduced by opening of the eyes and with hyperventilation and corresponds to rapid progression of the disease progress, and is more frequently observed in children. Completely disorgan-

ized records are observed in the terminal stages of the posterior fossa lesions.

The age of the patient and the rapidity of the progression rather than the size or pathological nature of the tumor determines the severity of the EEG alteration.

19. Localized paroxysmal electrical activities in recent, closed head injuries. Their diagnostic and prognostic values. — J. Courjon, Lyon.

Localized paroxysmal discharges without any clinical symptomes were observed in 10 recent head injuries, and most of the time these changes were transient. They occupied mainly the occipital region in the form of slow waves, spikes of pseudo-rhythmical spike and wave discharges. These patients were most of the time in light coma and preserved responses to sensory stimuli in the form of paroxysmal slow waves which in general were symetrical over both hemispheres. In a third of the cases, anatomical lesions were discovered. Clinical progress was favorable in seven of these ten patients, but two later developed seizures. The location of the focus was identical in these cases to that of the initial paroxysmal disturbances.

The discharges recorded in patients suffering from immediate post-traumatic seizures (most often in the form of epileptic status of focal origin) were more diffuse. The immediate progression was more severe.

One can consider the subclinical discharges as merely the minor form of those which are accompanied by clinical attacks. The difference is perhaps related to the severity of the cortical lesion, and also to the localization of the discharge. French *et al.* have indeed shown that the Rolandic region is by far the cortical area most sensitive to electrical stimulation. These paroxysmal electrical activities are the expression of a cortical lesion which cannot always be shown by arteriography. These changes do not imply necessarily any immediate serious prognosis, but the prognosis for the distant future has to be guarded because of the possibility of later clinical attacks which may occur as sequelae of the original trauma.

20. Clinical and EEG signs of "digestive epilepsy". — M. Bonduelle and C. Sallou, Paris.

The authors studied the clinical and EEG signs of a form of epilepsy called ''digestive'' on the basis of 7 observations (5 children and 2 adults) presenting epilepsy with painful abdominal manifestations.

Definition:

The purely clinical term ''digestive epilepsy'' has to be restricted to cases showing a predominance of digestive phenomena which are severe enough to consider the possibility of an abdominal affection (this raises the same semantic problem as for all the other varieties of so called visceral epilepsies). It is necessary to exclude from this group, the digestive manifestation, for instance salivation and nausea, which accompany a great number of epileptic attacks as other vegative phenomena, and will always remain in the background of the clinical picture.

Also to be excluded are sensory epilepsies and clonic seizures localized to the abdominal wall, which have been reported to occur.

Clinical signs:

The pain is the major clinical symptom accompanied by vomiting and nausea and sometimes by defecation. More characteristic than this polymorphus symptomotology without rhythmic time course (not really simulating a digestive affection) are the following criteria:
the paroxysmal occurrence;
the occasional or past occurrence of epileptiform manifestations brought out by the history consisting either of loss of consciousness or convulsive attacks following a digestive disturbance or alternating with it, in which case the diagnostic problem is easy; or manifestations reminiscent of psycho-motor attacks; or
the more discrete signs of pallor during and somnolence after the attack.

In cases where the signs are discrete, rare or without any evident relationship to the digestive phenomena, the diagnosis is often that of a truly digestive disease. This diagnosis however is never satisfactory, even when repeated examinations are carried out. Very often it is only when later other epileptic manifestations occur, that the patient is referred to a neurologist.

EEG signs:

In the seven cases reported here, three types of electrographic patterns were observed:

(1) Four times generalized changes without localized signs of a type usually associated with ''essential'' epilepsy.

(2) On 1 occasion alterations of the petit-mal type with paroxysmal discharges of 3 c/sec. spike and wave complexes.

(3) On 2 occasions asymmetrical records with unilateral changes, however without a typical focus, in either temporal or frontal regions, as has been reported by other investigators.

The distribution of electrical abnormalities as seen in the above grouping, is in accord with the notions now admitted concerning the digestive representation on the cortical surface, and the role of the hypothalamus in the control of digestive activities.

21. Electrographic studies of syncope: (I) correlation between electrographic and clinical signs in 100 subjects with vasovagal syncopes. — H. and Y. Gastaut, P. Navarranne, M. Pitot and V. Rueda-Galvis, Marseille.

All tracings were within normal limits, contrary to the opinion of Williams and Kershman, which found predominance of rapid rhythms and of slow rhythms respectively in patients with syncope. In no case was there any electrographic element characteristic of generalized or partial epilepsy. Furthermore, in no case did the Cardiazol activation prove the presence of an epileptic disorder, though on several occasions the syncope was precipitated with small quantities of Cardiazol. Compression of the ocular globes produced a cardiac pause of 3 sec. duration or longer in more than half of the cases. In 20 cases the pause was longer than 8 to 10 sec. and was accompanied by clinical and electroencephalographic signs of syncope.

Conclusion

From the theoretical point of view it seems that vasovagal syncopes have no relationship with epilepsy, not even with its ''borderland''. However, it seems

that they are in relationship with a common state of vagal hyperreactivity which is well demonstrated by the oculo-cardiac reflex.

From the practical point of view it seems that the subjects suffering from syncopes are often directed to the electroencephalographer where they often raise a diagnostic problem as important as that of epilepsy. The solution of this problem is considerably facilitated if one systematically investigates the oculo-cardiac reflex with EEG and EKG recordings. It is however, not necessary to use Cardiazol injection, although it is interesting to know that it ''activates'' the syncopes in the same way as it does epileptic attacks.

22. Electroencephalographic studies of syncope: (II) Electrical and clinical correlation in twenty subjects recorded during an attack of vasovagal syncope. — H. Gastaut, E. Lugaresi and M. Fisher-Williams, Marseille.

All syncopal attacks were accompanied by a cardiac pause of long duration which occurred during compression of the ocular globes (immediate syncope) or 10 to 16 sec. after the compression (delayed syncope).

The succession of the electroencephalographic, electrocardiographic, electrodermographic and clinical events, which precede an attack of delayed syncope allow to establish their relationship with a complex neuro-humoral mechanism, which itself is dependent upon activities and reactions of sympathetic and vagal origin. The immediate syncopes, on the contrary, seem to depend upon a direct nervous mechanism of reflex nature.

The different manifestations of syncopes depend upon the duration of cardiac arrest: up to a duration of 6-7 sec. of cardiac arrest there are no EEG or clinical effects; from 8 to 12-13 sec. there appear bursts of slow waves with more or less marked clouding of consciousness, above 14-15 sec. there appears a tonic opisthotonic contraction often preceded and followed by one or two generalized myoclonic jerks, but never accompanied by a real tonic phase. This contraction is accompanied by flattening of the record, preceded and followed by bursts of slow waves.

The convulsive manifestations of syncopal attacks are therefore different from those of generalized epilepsy both from the electrographic and clinical point of view. They are more similar, on the contrary, to tonic attacks of cerebellar origin and to decerebrate rigidity. They seem to depend, like the experimental attacks of anoxia provoked by Noell and Dombrowski and Ward, upon a telencephalic depression with release of functions integrated in the reticular formations of the lower brain stem.

23. Electrographic and clinical study of provoked attacks: a method of study and diagnosis of epilepsy. — H. Gastaut, M. Vigouroux and C. Alvim-Costa, Marseille.

The authors emphasize the practical and theoretical importance of this method, with which they have provoked during ten years more than 2,000 partial attacks without any untoward accident. The recorded discharges can be broken down into two groups according to the topographical distribution of the recorded discharges:

(1) Localized discharges with the aspect of rhythmic spikes, usually seen in temporal or parieto-occipital regions and not necessarily accompanied by clinical symptoms in correlation to the functional significance of the firing territory (as e.g. visual disturbances of an elementary nature would be in occipital discharges). The epileptogenic lesions when they are identified do not necessarily correspond in location with that of the paroxysmal discharges (thus the majority of occipital discharges are obtained in psycho-motor epileptics with normal visual fields and in whom the inter-critical EEG focus is localized in the anterior temporal region. Similarly, epileptics with a left temporal focus sometimes show paroxysmal discharges during attacks in the right temporal region).

(2) Focal discharges producing a diffuse change in the electrical activity, either in the form of dysynchronization or slow hypersynchronization involving the whole extent or parts of one or both hemispheres. (Fronto-temporal regions most often.) These discharges are usually accompanied by automatism and confusion and occur in subjects with an anterior temporal focus.

(3) Finally, there are cases where during the same attack, localized and diffuse discharges become associated with each other in independent or concomittant, temporal and spatial relationships, with or without phase relations, mostly occurring in territories usually comprising the anterior temporal region, the frontal region, or the posterior temporal and parietal area. Clinically these complex attacks are usually of a psycho-motor type.

Conclusions

The knowledge of the clinical phenomena is essential for development of epileptology. It allows a new physio-pathogenetic classification of the epilepsies which is more valid than the one based on the ''static'' basis of inter-critical discharges. It allows a quantitative redistribution of the different types of epilepsy. (Rarity of seizures of frontal, central, parietal and occipital origin secondary to local lesions, whereas there is a great number of attacks propagated to a distance from lesions responsible for psycho-motor epilepsy.)

This also allows to refute the inaccurate postulate as to the localizing value of the ''signal symptom''. (The majority of the occipital discharges with simple visual manifestations, depend upon anterior temporal lesions, whereas the majority of somato-motor attacks occur without lesions in the rolandic area.) This finally allows to define more precisely the indication for surgical operation (presence of paroxysmal seizure discharges on the side contra-lateral to that of the ''inter-seizure'' focus).

24. Electrographic status epilepticus and integrity of psychical functions: report of a case. — L. Rouvès and C. Rouvès, Saint-Etienne.

During prolonged epileptiform paroxysmal discharges of diffuse distribution and spike and wave morphology there is almost always a disturbance of consciousness, sometimes clearly manifest, and at others only discovered by refined testing. According to the accepted opinion all cases with electrographic status showing diffuse spike and wave discharges are associated with a disturbance of consciousness varying between a slight clouding, to the most complete mental confusion. The case reported by the authors seems to be different from these general rules.

The patient was a man of 45 years of age, who previously had only presented rare and brief generalized convulsive seizures since the age of 12 years. A systematic electroencephalographic examination was carried out. The tracing was characterised by a succession of multiple spike and wave complexes of a rhythmical character interrupted by only very brief intervals of normal tracings no longer in duration than 5 sec. The epileptic abnormality was not modified by hyperventilation nor by opening of the eyes, nor by any stimuli applied in an attempt to render the patient more aroused. The patient did not show any behavioral disturbances. His conversation was clear and there were no deficiencies in calculation and reading, nor any signs of the slightest disturbance of consciousness. With intermittent photic stimulation, almost immediately a generalized convulsion with predominantly clonic contractions was precipitated and shortly preceded in the EEG by a disappearance of spike and wave discharges. The mental functions returned rapidly to normal in parallel with the recovery of the EEG.

The authors emphasize the following points: this adult male never had any minor epileptic manifestations not even during childhood. There was complete absence of any disturbances of consciousness, during a period of electrographic status, with diffuse spike and wave discharges. This case is compared to another case observed by the authors in a child of 2 years, in whom the EEG was recorded while the patient showed mental confusion.

25. Electrographic changes in epileptics under Pentothal. The participation of the reticular formation in control of epileptogenic discharges in man. — J. Schneider and G. Thomalske, Colmar.

The progressively activating and then depressive action of Pentothal upon the reticular system was studied in 100 subjects suffering from varied epileptic manifestation (centrencephalic attacks, generalized convulsive seizures, due to large and deep focal epileptogenic lesions involving cortical and subcortical structures outside the rhinencephalon, psychomotor epilepsies of temporo-rhinencephalic origin, focal epilepsies due to lesions on the cortical surface, or immediately below, but outside the temporal region).

Three aspects of the disturbances presented by these patients were studied:

(*a*) the electrographic disturbances of the stage of rapid electrographic activity (stage of sleep induction and of reticular activation) and of the stage of K complexes (stage of deep sleep) occurring characteristically in the epileptic patient were observed. These disturbances were characterised by the absence of a stage of rapid activity, the presence of paroxysmal dysrhythmic phenomena and by modification of the Pentothal-induced K complex;

(*b*) inhibitory and facilitatory changes of spontaneous epileptic discharges were seen during the period of activation and of depression of the reticular formation as induced by Pentothal;

(*c*) the modification of responses to sensory stimulations of sufficient intensity to produce an electrographic or clinical and electrographic arousal response were studied.

On the basis of these electrographic, clinical and neurophysiological data the authors propose a classification of epileptic attacks occurring predominantly or exclusively during sleep.

26. Clinical epileptic manifestations during treatment by chlorpromazine. — P. Soucachet, P. Doussinet and B. d'Alteroche, Clermont-Ferrand.

The activating effect of chlorpromazine (Largactil) in epileptic patients and more specially in patients with temporal lobe epilepsy is reported by the authors, who had the opportunity to observe a certain number of clear cut cases which form the basis of this report.

In the women's section of the Psychiatric Hospital of Sainte-Marie in Clermont-Ferrand under the direction of Dr. Doussinet, more than 400 patients were treated with chlorpromazine. Among these 400 patients 14 presented epileptic manifestations. These 14 patients never before had any epileptic episodes. During their treatment with chlorpromazine 5 had typical clinical attacks and others minor episodes which suggested the possibility of an epileptic disturbance, such as vertigo, absences, nocturnal involuntary micturition.

It is however necessary to point out that though none of their patient had given any history or signs of epileptiform disturbance, all had been subjected to intense therapeutic procedures. Ten among them had received electro-shock therapy and 4 among them had been lobotomized. However, all EEG examinations were carried out more than six months after the last electric shock and 4 never had any electroshock treatment. All patients had been hospitalized for a long time, and no suggestive evidence of epileptic abnormality was ever encountered before they were placed under chlorpromazine therapy.

This drug was administered in all cases by mouth in moderate doses, varying from 75 to 200 mg. but in all cases this therapy was carried out during prolonged periods of time, which were never shorter than two months.

From the electrographic point of view three observations deserve mentioning:

(1) the types of abnormality recorded were fairly uniform. In all cases they were recorded from the temporal regions in the form of polymorph delta waves of more or less continuous character, spikes or bursts of dysrhythmic activity. These disturbances were either bilateral or unilateral, but in the latter case often switching from one side to the other between successive examination, as is often seen with temporal lobe epilepsy;

(2) after withdrawal from chlorpromazine medication, the electrographic abnormality regressed, but only very slowly, over a period of 2 to 5 months following the discontinuation of the treatment. In certain cases when the treatment produced a clinical improvement of the syndrome, the reappearance of clinical psychiatric manifestations occurred when the tracing began to improve. The electrographic disturbances were seen to diminish when Gardenal (Luminal) at a dose of 5-10 cg. was added to the chlorpromazine treatment. In some cases the electrographic abnormalities regressed on discontinuation of the chlorpromazine treatment, but reappeared when the treatment was reinstituted;

(3) in view of these findings, it was legitimate to suppose that minor disturbances might be encountered in other patients treated with chlorpromazine. Thirty patients in which no clinical evidence for any epileptiform disturbance was present were picked out at random. Twelve among them showed the same type of abnormality, but generally in a more attenuated form. The authors conclude that it is

necessary to be cautious in administering chlorpromazine, that EEG control seems to be necessary when this treatment is given for a prolonged period of time. Additional prophylactic administration of Gardenal is indicated in cases where the electroencephalogram shows abnormality.

27. Electroencephalographic studies of several activating substances. — G. and J. Verdeaux, G. Drossopoulo and P. Chanoit, Paris.

The activation of the EEG by different drugs (chloralose, Metrazol and Megimide) in a great number of epileptic and non-epileptic patients led the authors to define certain rules which should guide the use of these products.

The practical interest of chloralose is limited to diagnostic investigations of petit mal if the diagnosis is not revealed by classical activation procedures (hyperventilation and intermittent photic stimulation).

The results obtained with Metrazol are well known, and comparable to those obtained with Megimide.

The authors, however, prefer the latter product because it is more easily handled, allowing to observe the attack more acurately and because it does not produce anxiety. Despite its slow and progressive action, it is possible to reach a critical stage.

The attacks thus obtained by activation do not always allow a precise diagnostic conclusion, but their observation is essential for an electrographic and clinical study in certain patients.

This study showed that a simple determination of the threshold is never sufficient in view of the inconstancy of a temporal relationship between the first paroxysmal disturbance and the onset of the attack.

When this study is applied to patients in which the diagnosis of epilepsy was not made or remained doubtful, only the precipitation of a minor electrographic attack accompanied by corresponding clinical manifestation allows to affirm or to revise the diagnosis. However, the possibility of seizures of a very focal nature occurring in deep structures has to be considered since presumably such a seizure might occur, without any appreciable electrical disturbance recorded from scalp electrodes.

28. The modification of the response to intermittent photic stimulation in patients suffering from hallucinations or from a syndrome of "automatisme mental". — C. Leroy, Paris.

The patients of the Villejuif Hospital were examined according to a standard technique. Twenty-one electrodes assembled in 7 tripodes were used, records were taken with a ECEM EEG apparatus, a Epiphote stroboscope was used for photic stimulation, which was applied during opening and closure of the eyes using simple and twin flashes for more than 3 min.

The posterior tripode electrode assembly is placed as follows: the postero-inferior electrode rests at a point 1 cm. above and outside of the occipital protuberance and therefore close to the calcarine fissure. The postero-superior electrode above the latter, at 1 cm. lateral to the mid-sagittal plane. This position is the one which gives the best record of the driving response. The temporal tripode assembly is placed in the usual fashion.

Under these conditions the authors observed that in a considerable number of patients with chronic delusions responses at the second harmonic or more rarely at the first sub-harmonic frequency were recorded in the anterior occipital and parieto-occipital regions, whereas the posterior occipital responses remained at the fundamental frequency. The more frequent types of responses were at 16 c/sec. for 8 c/sec. stimuli and even more frequently 18 c/sec. responses were seen for 9 c/sec. stimuli. These responses are remarkable by their fluctuations in time and space and appear often only for 2 or 3 sec., then disappear and later reappear again. While they occur the patient most often shows signs of lively interest for the stimulation. Much more often than other patients, these subjects experience this type of stimulation as "pleasant" or "nice" or "frightening". Sometimes the "pleasure" evoked by this stimulation changes into anxiety with the change of frequency of the stimulation.

These reactions are not pathognomic, since occasionally they were also encountered in other patients, for instance in hysterical women and in a case of depression which appeared several years after severe intoxication by carbon monoxide. Nevertheless, the correlation with the syndrome of "automatisme mental" seems to be quite clear.

These responses have been distinguished from the second harmonic and sub-harmonic responses observed in normal subjects after opening and closing of the eyes, which is a generalized response, whereas in these patients one simultaneously records a direct response.

The lability and richness of the various rhythms of patients with chronic delusions is astonishing. This is in contrast with the irregularity and homogenisation of the tracing seen under chlorpromazine which goes along with extension of the field of background rhythms to the detriment of some slow rhythms.

In a work carried out with D. Sigwald the authors demonstrated that chlorpromazine favored the appearance of myoclonic discharges in response to intermittent photic stimulation essentially on the basis of a recruiting phenomenon.

In chronic delusions there might be hyperactivity in the association systems which becomes reduced with augmentation of recruitment under the effects of chlorpromazine.

29. The differences in electroencephalographic abnormalities of two forms of myxoedema in childhood, one due to thyroid insufficiency, the other to a cerebral disorder. — P. Passouant, J. Cadilhac and R. Jean, Montpellier.

In 20 children of 2 months to 4 years of age, suffering from congenital myxoedema electroencephalographic examinations carried out jointly with other diagnostic methods, such as biological and biochemical investigations allowed to differentiate two types of myxoedema, one due to a thyroid insufficiency and the other due to an encephalopathy. The evolution of these disorders could be followed. Differences in the EEG patterns could be established:

(*a*) in myxoedema due to thyroid insufficiency (10 cases) the EEG shows slow activity of low voltage and demonstrates a clear retardation of cerebral maturation;

(*b*) in myxoedema due to an encephalopathy (10 cases) there are signs of localized or generalized organic brain disturbance with the most frequent

occurrence of abnormal activity being recorded from both frontal regions.

The EEG changes induced by thyroid treatment show different effects upon the EEG in the two conditions.

In myxoedema due to thyroid insufficiency the hormonal treatment produces a marked improvement of electrical activity with acceleration and stabilisation of the background rhythms. When this treatment is insufficient or instituted too late, there remains a residual defect in maturation of the EEG, which is associated with a marked mental retardation.

In the myxoedema of cerebral origin, only little effect of the hormonal treatment upon the EEG is noted. This mainly applies to the signs of localized cerebral damage, or to irritative abnormalities.

The significance of the EEG in relation to the etiology of infantile myxoedema is discussed, especially the effects of cerebral lesions and of anoxemia of the tissues. In cerebral myxoedema the anoxia associated with the hypothyroidism certainly contributes to the primary encephalopathy.

30. Electroencephalograms of patients with tuberculosis treated by cycloserine. Correlation of the EEG alterations with signs of clinical intolerance. — P. Nayrac and M. Beaussart, Lille.

The purpose of this study was to evaluate the modifications of the EEG by ingestion of cycloserine and to correlate these changes with the clinical symptoms in cases of intolerance to the drug. All cases were eliminated where the EEG was already abnormal before the treatment was instituted.

Thus only 9 cases in children and 3 in adults could be used for this study.

Changes seen in children. In the first group 5 cases without signs of intolerance and 2 with minor changes of behavior leading to some agitation, the tracing remained unchanged. The second group included 2 cases who had convulsive attacks. In one case two seizures occurred within 48 hours 10 days after the cessation of the treatment, and in the other, one attack six months after the initiation of the treatment. In both cases, the most interesting abnormality consisted of an early appearance of slow waves at 2-3 c/sec. occurring in posterior head regions upon closing of the eyes.

Changes seen in adults. In the three cases studied similar modifications with the same time sequence of development were observed, ten days after the beginning of the treatment, the alpha frequency became slower and 6 c/sec. activity appeared diffusely over both posterior head regions. Fifteen days later this increased slow activity was even more marked, and 3-4/sec. slow waves were seen. Still 15 days later, the tracings returned to the aspect they presented before any treatment was introduced.

The following conclusions were drawn: in the case of the two children which presented convulsive seizures electroencephalographic abnormalities occurred early and independently of the date of onset of seizures. This probably indicates that there was some pre-existing hyper-excitability.

In adults it seems that some adaptive mechanism developed which counter-acted the disturbances produced by the ingestion of cycloserine.

31. A contribution to the study of periodical paroxysmal discharges in the EEG. An observation on two unusual cases. — P. Nayrac and M. Beaussart, Lille.

The periodic occurrence of paroxysmal discharges which is particularly spectacular in cases of sub-acute sclerotising leucoencephalitis, was also seen in other conditions characterized by organic lesions associated with an inflammatory process. The correlation between this periodic disturbance in the EEG and the organic process is evident.

However, the authors observed two cases in which no organic alteration could be detected by various diagnostic procedures. One case presented generalized seizures with all the earmarks of an idiopathic epilepsy. All abnormalities disappeared eight days after the beginning of barbiturate treatment. The second case was a chance discovery during the EEG examination of an 11 year old child who presented signs of retardation of mental and sexual development. The EEG abnormalities in the first case manifested themselves in the form of short generalized bilaterally synchronous bursts of one or two spike and wave discharges, or multiple spike and wave discharges, followed by two or three slow waves. In the second case numerous short bursts of slow waves and multiple spike and wave discharges of 2-2½ c/sec. were seen, which only were observed over the right hemisphere with maximum discharge consistently localized to posterior temporal regions.

The authors compare the periodic disturbances in these two cases with those where organic alterations are known to exist.

32. EEG findings in encephaloses. — P. Passouant, J. Cadilhac, W. Walter and E. Moretti, Montpellier.

This study deals with 15 patients suffering from presenile cerebral atrophy of the Pick or Alzheimer type. The diagnosis was based on clinical signs (progressive dissolution of mental activities with memory disturbances and disturbances of wakefulness — aphasia apraxia, agnosia, convulsive and extra-pyramidal manifestation), and upon pneumoencephalographic findings (ventricular dilation and cortical atrophy). In all cases the disturbances of the cerebral background rhythms were found. There was either a diffuse slowing of the background rhythms, or signs of a localized disturbance, or bilateral frontal delta activity.

Epileptiform abnormalities were seen in routine recordings in the form of sharp waves recorded in temporal and frontal regions and occuring in bilateral synchronous discharges. These abnormalities were sensitive to Cardiazol and they were also confirmed in sleep recordings.

The presence of disturbances in mechanisms of wakefulness were shown by the abolition of the blocking reaction to visual stimuli when the patient was awake and by the absence of cortical responses to auditory stimuli during sleep. Furthermore, the sleep tracing was rather featureless and monotonous and did not show the habitual fluctuations.

These abnormalities are reminiscent of those observed in encephalitis and indicate a marked involvement of the subcortical regulatory systems. They constitute objective proofs for the presence of epileptic abnormalities frequently seen in these patients, though often only in a minor form. These EEG findings also demonstrate the disturbances associated with the patient's confusion.

33. Clinical and EEG diagnostic of acute necrotising encephalitis. Its interest in the study of cerebral abnormalities centred upon rhinencephalon. — J. Radermecker, Antwerp.

The author had the opportunity to study at the anatomical and pathological laboratory of the Bunge Institute, the autoptic materials in 12 cases of acute necrotising encephalitis. Most of these observations have never been published before, and the cases are studied by different observers. The similarity of clinical course is most striking. The disease starts by an apparently banal infection episode with involvement of the upper respiratory tract, the digestive tract or the urinary system. Then a modification of the personality appears with disturbances of consciousness and progressive development of a stuporous state. The patient becomes bizarre, apathetic or in other cases he is anxious and agitated with periods of confusion and dream like states, or he presents a psychotic picture with tendency to suicide. Often some olfactory, auditory or other hallucinations appear before the patient becomes confused. When the patient is confused, there are often some epileptic attacks with no clear focal signs, mostly involving the motor system. Upon lumbar puncture in a certain number of cases some lymphocytosis was noticed, but this may be absent. In the early stages, the disease produces some fever. Death occurs due to cardiac and pulmonary causes or in coma with or without hypothermia. This most often happens between the 5th and the 20th day of the disease. In certain cases the course may be much longer with transitory remissions and exacerbations.

The inflammatory necrotising process involves the tips of the temporal lobe, the posterior part of the orbital gyri, the rhinencephalic areas, the hippocampus and the cingular gyrus. From these regions bands of necrotic tissue extend into the hippothalamus and into the sub-ependymal layers. The insula is regularly involved. Similar lesions are sometimes, but not regularly seen on the convexity of the brain, in the first frontal convolution, along the interhemispherical fissure, in the second and third temporal convolution, the parietal region and adjacent area of the angular gyrus. One also observes small disseminated lesions in the form of glial and perivascular infiltrations in the hypothalamus, the nucleus dentatus, in the higher brain stem and even sometimes in the medulla oblongata. These disseminated glial lesions are small in comparison with the necrotising lesions.

The EEG which was obtained in 4 of these patients showed a slow polyrhythmia of a variable degree of severity, as seen in all encephalitic processes. Furthermore there were areas of flattening of the record and large delta foci usually in the temporo-insular region. The pattern is also characterised by some epileptiform discharges in the form of slow spikes, often of a repetitive character recorded in the same areas.

The author stresses the diagnostic importance of the clinical and EEG symptomatology in this form of encephalitis, or specific inflammatory cerebral reaction commonly described as acute necrotising encephalitis.

The interest of this particular electrographic and clinical symptomatology is also pointed out in view of the fact that the lesions predominantly involve the formations of the rhinencephalon.

34. EEG findings in certain tropical forms of encephalitis. — G. Miletto, G. Cardaire, A. Pelissier and J. Bert, Marseille.

The authors present observations of electroencephalograms in cerebral diseases typical for the tropics or at least very rarely seen in France.

Leptospiroses. EEG abnormalities are in relation with the azotemia.

Benigne multirecurrent meningitis. The abnormalities in the EEG disappear with clinical recovery.

Encephalitis type B. Very slow polyrhythmia. The rapid rhythms in anterior head regions observed by others could not be confirmed.

Encephalitis following rabies vaccination. The disease appeared one year after vaccination. The clinical symptomotology was characterised by spasms and flexion. The EEG showed hypsarhythmia.

Ricketsia encephalitis. This was a case of scrubb-typhus with transient epileptiform sensitivity to photic stimulation.

Two cases of typhus fever were seen, one with a transient myoclonic epilepsy and the other with a pseudo-idiopathic epilepsy.

Leper. When mental disturbances were present, simple desynchronisation of the EEG was seen.

Trichinosis. Six cases with normal EEG.

Shigellosis. Slow dysrhythmia with irritative elements followed by marked sequelae.

Disseminated nervous system parasitoses. Very variable tracings.

Disseminated cysticercosis. No localized signs.

Distomatosis. No signs during dissemination.

Cerebral form of haematobium shistosomiasis: One case with psychomotor epilepsy.

Details reports on these observations are going to be published in *Médecine Tropicale* in 1957.

35. EEG changes in three patients with epilepsy due to post-vaccinal encephalitis. — J. N. Vallat and J. M. Lepetit, Limoges.

The authors presented a series of EEG tracings carried out in three patients who suffered from encephalitis consecutive to smallpox vaccination. The epilepsy was the major sequela of this disease.

Both patients were adults and presented tonic-clonic generalized attacks associated with absences, or "sub-clinical absences", as judged by reaction time measurements.

The third patient was a child who suffered from bilateral myoclonic convulsions and adversive fits.

Repeated EEG examinations during the month following the acute phase of the disease showed the following changes: (*a*) non-specific abnormalities in the form of high voltage slow waves occurring in bursts and slow diffuse dysrhythmia with a vague focalization of sharper potentials; (*b*) abnormalities more specific for epilepsy, in the form of spike and wave complexes, or multiple spike and wave discharges of a bilateral distribution.

These EEG findings allowed not only to make the correct diagnosis but also guided the therapeutic measures which were instituted, while at the same time acting as a control measure to evaluate this therapy.

These three electroencephalographic and clinical observations of epilepsy due to post-vaccinal encephalitis invalidate the classical notion that neurological sequelae are rare after this form of encephalitis.

PRINTED IN CANADA

THE SWEDISH CLINICAL NEUROPHYSIOLOGICAL SOCIETY

Serafimerlasarettet, Stockholm

December 7, 1956

Secretary: L. E. LARSSON

Department of Clinical Neurophysiology,

Serafimerlasarettet, Stockholm, Sweden

1. The influence of hypothalamic thermodetectors on cortical and motor activities. — CURT VON EULER and ULF SÖDERBERG, Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm.

The influence of hypothalamic and body temperatures on the EEG and gamma motor system was studied in cats and rabbits. Index of gamma motor activity was obtained by recording muscle spindle discharge from a muscle at constant tension.

Moderate hypothalamic heating inhibited the gamma motor activity in both cats and rabbits. Excessive hypothalamic heating induced increased discharge frequency in muscle spindles in rabbits. Moderate heating inhibited shivering in both species and induced cutaneous vasodilatation as well as other autonomic activities. Excessive heating induced restlessness in rabbits.

Moderate hypothalamic heating synchronized the EEG in both cats and rabbits. Excessive heating desynchronized, ''aroused'', the EEG in the rabbits.

Simultaneous records of muscle spindle activity and EEG have demonstrated a close correlation between these two events. Anaesthetics abolished more readily the influence of hypothalamic heating on EEG than on the gamma motor activity. Other exceptions from the correlation were also discussed.

It is concluded that the effects of hypothalamic heating are mediated by common relays influencing both gamma motor and cortical activity. Hypothalamic thermoceptive structures may thus, like most peripheral receptors, be projected upon the activating relay system of the brain stem. The muscle spindle test has been found to be a useful index of that system.

Activation of the central cephalic relay system by various means was found to elevate the threshold temperatures for thermoregulating reactions with increased body temperature as the result. Correspondingly inhibitory reflexes lowered the threshold temperature for thermoregulatory events resulting in a fall in body temperature. Thus a mechanism is demonstrated for the ''setting'' of the ''body thermostate''.

The significance of the results for homeostasis of body temperature were discussed.

2. The cerebral blood flow during different EEG responses elicited by brain stem stimulation. — DAVID H. INGVAR, TORSTEN KRAKAU and ULF SÖDERBERG, Department of Physiology, University of Lund, Lund, and the Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm.

Measurement of the cerebral blood flow was carried out in anaesthetized or ''encéphale isolé'' cats and the effects upon the EEG and the blood flow were studied after electrical stimulation of the brain stem. The usual EEG ''arousal reaction'' (cortical activation) with an increase of frequency and a retention or increase of amplitude was followed by a marked increase of cerebral blood flow due to a reduction of the cerebral vascular resistance.

Another type of response to the brain stem stimulation consisted of a flattening of the EEG with only occasional slow waves. In most of these cases there were no significant cerebral circulatory changes. This type of response could not be explained as due to changes in respiration, in muscle tone or in systemic circulation. It also seems very unlikely that local cortical circulatory changes (vasoconstriction) could explain it. Anaesthesia was not found to be a prerequisite for the ''flattening reaction''. It is suggested that this type of reaction to brain stem stimulation, as well as the ordinary ''arousal'' (activation) of the EEG, both represent physiological events.

A sleep pattern could also be induced in the EEG by electrical stimulation of the brain stem. No cerebral vasomotor changes were observed when this pattern appeared.

Some of the reactions described were also studied by optical frequency analysis *ad modum* Krakau (1951) and the correlation in time between the frequency of the EEG and the cerebral blood flow was determined.

3. Activation with Megimide ($\beta\beta$-methyl-ethyl glutarimide) in electroencephalographic investigation of epileptic conditions. — S. FLODMARK, I. PETERSÉN and K. STENBERG, The Clinical Neurophysiological Laboratory, Sahlgrenska sjukhuset, Gothenburg.

Since the beginning of 1956 we have tested Megimide as an activating agent in electroencephalographic examinations.

We used a 0.5 per cent solution, injected at the rate of 2 cc. (10 mg.) per min. Generally we did not give more than a total of 100 mg. or 2 mg/kg. body weight. After activation, in the event of seizures or of marked paroxysmal activity on the EEG, we administered 1-2 cc. narcotal intravenously. Prior to electroencephalographic investigation no anticonvulsants had been administered for 1 to 2 days.

We used Megimide in 50 patients with the diagnosis of epilepsy — 33 of focal and 17 of non-focal type, the latter category including those with petit mal and bilaterally synchronous wave and spike activity.

The effect of activation was divided into two groups:

1. Effect on the activity present before injection of Megimide. An activating effect on the EEG was obtained in 75-80 per cent of the cases (about the same effect as that reported by Cure *et al.* (1948)

in respect of Metrazol, administered by slow intra venous injection). The abnormal activity thus showed an increased amplitude and, moreover, it occurred to a greater extent than before injection of Megimide. In 13 cases with electroencephalographic focal abnormalities both sharp waves and slow waves of theta and delta type were found in the same focus. Megimide activated each of these types of abnormalities at the same dose.

The amplitude of the basic activity often increased, too, after Megimide. No arousal effect consisting of desynchronization of the basic activity was observed on the EEG.

A few cases presented, on one and the same EEG, both bilaterally synchronous 3-4 per sec. wave and spike complexes and a focal abnormality. Here Megimide activated these complexes before the focal abnormality. Analysis of the series showed that focal abnormality was activated at a mean dose of 0.8 mg. per kg., but nonfocal abnormality at a mean dose of 0.5 mg. per kg.

2. In 15 cases, not only did the existing activity increase, but some new type of activity appeared. In some of these patients the new activity was such — e.g., short bursts of bilaterally synchronous waves of theta or delta type — that its diagnostic significance could not be evaluated with certainty. In other cases the new activity was more characteristic. Thus three cases presented a focal abnormality with slow waves. After Megimide, sharp waves too appeared in the same focus. In two patients with the clinical diagnosis of petit mal, Megimide was followed by bilaterally synchronous 3 per sec. wave and spike complexes that were not found in the resting EEG or in hyperventilation.

In 8 cases Megimide produced some form of seizure: grand mal in 2, absences in 4, and psychomotor attacks in 2. Insofar as the clinical picture of previous seizures was known, Megimide elicited a duplicate of it.

In 20 patients (some with epilepsy and the remainder with nervous diseases other than epilepsy), activation was done both with Megimide and by the slow method with 2 per cent Metrazol. These patients were closely questioned as to their subjective symptoms, which in both methods were found to consist of dizziness, anxiety and nausea; in addition to which seizures might occur. The two methods of activation showed no statistically significant difference with respect to these symptoms.

Summarizing, activation with Megimide in this small series had an effect more or less similar to that which has been observed in activation with Metrazol. Drossopoulo *et al.* (1956) have reported a somewhat more favourable impression of Megimide as an activating agent in electroencephalographic examinations.

4. Electromyographical investigations of myasthenia gravis. — A. LILJESTRAND, Stockholm.

THE EEG SOCIETY

The National Hospital, Queen Square, London, England

January 5, 1957

Secretary: Dr. S. L. SHERWOOD

Medical Research Council Laboratories, Holly Hill, Hampstead, London, N. W. 3

1. Electroencephalography in the newborn. — R. F. HARRIS, K. RHODES, J. P. M. TIZARD and W. H. C. WALKER, Postgraduate Medical School, Hammersmith Hospital, London.

Electroencephalography has been carried out, and in many cases repeated at intervals, in 50 newborn babies. The objects of the investigation, which is continuing, are firstly to obtain EEG records in normal babies for comparison with those done in cases of neonatal convulsions, and secondly to investigate whether or not the EEG will prove to be of any value in predicting the outcome of brain disorders in the newborn period.

We propose to discuss: (1) the technique of electroencephalography in the newborn, and the problems we have encountered; and (2) the appearance of the EEG record in the newborn baby, under the conditions of our technique, with special reference to ''episodic sleep activity''.

2. Recent observations on the action of some drugs in relation to the reticular formation of the brain. — P. B. BRADLEY, Medical School, Birmingham.

Experiments in animals, using conscious chronic preparations carrying implanted electrodes and acute preparations (''encéphale isolé'' and ''cerveau isolé''), have shown that certain cholinergic drugs and acetylcholine antagonists, for example, physostigmine and atropine, produce effects on the electrical activity of the brain which do not correlate with behaviour, and that these effects are not abolished either by high spinal or mid-brain section (Bradley and Elkes 1953). Drugs such as amphetamine and d-lysergic acid diethylamide (LSD 25) produce effects on the EEG which correlate with behaviour and these effects are abolished by spinal (LSD 25) and mid-brain (amphetamine) transection, respectively. The alerting effect of LSD 25 was seen to be dependant upon environmental conditions, whereas that of amphetamine was not. These results led to the suggestion that amphetamine may act directly on the reticular formation, but that the action of LSD 25 might be more closely related to afferent collaterals entering the reticular formation at the brain stem level (Bradley and Elkes 1956). At the same time, it was suggested that the arousal system is probably not activated by a predominantly cholinergic mechanism.

Similar studies with chlorpromazine (Longo *et al.* 1954, Bradley and Hance 1955) have indicated that this drug probably has an action at the level of the reticular formation.

In recent experiments the effects of these drugs have been studied on arousal produced by stimulation

of the reticular formation, and, in some cases, arousal to afferent stimulation (Bradley and Key 1956).

The results obtained support many of the suggestions made previously. Atropine and physostigmine, although modifying EEG activity had no effect on behavioural arousal. Amphetamine progressively lowered the threshold for arousal produced by direct stimulation of the reticular formation and LSD 25, which had no effect on this threshold, lowered the threshold for arousal to afferent stimulation. Chlorpromazine appeared to have little direct depressant action when compared with barbiturates, but readily blocked arousal to sensory stimuli. Thus, it is thought that this drug may have an action related to afferent collaterals entering the reticular formation.

3. The mechanism producing tremor in healthy subjects: A review of the evidence. — A. M. Halliday, M. R. C. Neurological Research Unit, National Hospital, London.

The first experimental investigation of the mechanism responsible for tremor in healthy subjects was by Horsley and Schäfer (Schäfer 1886; Horsley and Schäfer 1886). They showed the existence of a 10 c/sec. tremor in voluntary muscular contraction and concluded from the results obtained by stimulating different parts of the motor system in animals, that the rhythm could be produced at spinal level. Later work, beginning with the observations of Jasper (1936) concentrated on the possible relationship of this tremor with the alpha rhythm recorded over the contralateral precentral area. Early reports of a close correlation (Jasper and Andrews 1938) have not been borne out by other workers (Travis and Cofer 1937; Lindqvist 1941; Friedlander 1952). Furthermore, the recent experiments of Sutton (reported in Hammond, Merton and Sutton 1956) have shown that tremor may behave in the opposite way to the alpha rhythm, and disappear on closing the eyes or on the withdrawal of a visual cue. Evidence has also been produced that the tremor rhythm is present in reflex movements occurring below the level of a clinically complete spinal transection due to transverse myelitis (Marshall and Walsh 1956).

Sutton's work emphasises the importance of the influence of higher centres in determining tremor amplitude, and this is also clear from the many previous investigations of the influence of anxiety and emotional stress upon tremor. But all these investigations leave undecided the site of the mechanism determining tremor frequency.

The tremor rhythm may represent:

1. An intrinsic rhythmicity of the spinal motoneurones or interneurones;
2. A rhythm reaching the motoneurones from a higher centre, not necessarily cortical;
3. A self-maintained oscillation due to servo-instability in the stretch reflex arc, or
4. A mechanical resonance of the trembling part.

Recordings of finger tremor in healthy subjects by a photoelectric method (Cooper, Halliday and Redfearn 1957), when subjected to automatic frequency analysis, have shown the constancy of the spectrum of tremor frequencies and its independence of the mechanical properties of the part (Halliday and Redfearn 1956) which dispenses with the last hypothesis. But neither this finding, nor the absence of any significant change in amplitude observed between two groups with more or less active reflexes (measured clinically as the tendon jerk) is against the servo hypothesis, as the behaviour of such a loop would be expected to be more or less independent of load and small changes in loop gain.

Other evidence seems to be more decisive. In a series of patients with *tabes dorsalis*, showing varying degrees of deafferentation, the most severely deafferented showed no characteristic tremor rhythm. Those partially deafferented, on the other hand, showed a much greater amplitude than normal (Halliday and Redfearn, unpublished). These results suggest that the presence of the afferent nerve fibres is essential to the normal tremor rhythm, which is against the first of the three hypotheses, if this is taken to apply strictly to the alpha motoneurones. To decide between the second and third hypotheses, an attempt has been made to see if the frequency alters with variation in the conduction delay round the loop, as would be expected on a servo hypothesis. The results of some preliminary experiments (Halliday, unpublished) in which tremor frequency has been measured with the limb at different temperatures, suggest that it does.

4. The blink reflex and its possible relationship to the photomyoclonic response in man. — W. A. Cobb and T. A. Sears, National Hospital, Queen Square, London.

Although corneal stimulation is most affective a blink may be reflexly evoked by any unexpected stimulus, irrespective of the sensation aroused; in more extreme examples of startle the blink is only part of a stereotyped pattern of movement and posture (Landis and Hunt): the progressive involvement of more of the musculature with increasing startle bears a striking resemblance to the recruitment seen in the photomyoclonic response to flicker.

The pathways serving blink and photomyoclonus in man are incompletely known and a first need is knowledge of the latencies involved. The responses to various stimuli have been studied, using the EMG of *orbicularis occuli* as the indicator of the blink. To light flashes of sufficient intensity to give near-minimal delay in the retinogram the latency is about 45 msec., various peripheral cutaneous stimuli give similar values, while the response to clicks is rather quicker, about 35 msec. The experiments of Kugelberg on the myotatic lid reflex have been repeated and show that the delay in the facial nerve (final common path) must be 5-6 msec.; this response can be facilitated by appropriately timed click or flash stimuli, the timing indicating that there is no convergence before the final common path. In conjunction with G. D. Dawson, using his averaging technique, the delay in the cortical response to flashes has been re-evaluated, the earliest response being at 25 msec.

These results show that there is time for the blink response to a flash to travel by way of the visual cortex, contrary to the observations of Bickford on the photomyoclonic response. During the experiments the importance of conditions of startle in determining amplitude, but not latency, of the response has been very apparent, so that the case with which a response can be obtained is a measure of the "set" of the subject. This observation may be compared with the view of Shagass that the photomyoclonic response "involves a normal mechanism for which ease of elicitation varies in relation to degree of deviant cerebral excitability"; in that it may be anatomically

more simple (the myotatic response) or complicated at will by paired stimuli to different systems, it is possible that study of the blink response might be rewarding as an indicator of one aspect of brain-stem reticular activity.

5. EEG and vasomotor adaptation to repetitive stimuli during sleep. — G. Pampiglione and Brian Ackner, Maudsley Hospital, London.

The usual EEG response to a mild alerting stimulus during sleep is an immediate K complex. This is often followed by a digital vasoconstriction with a delay of 3-4 sec. In our preliminary observations, reported to this Society two years ago, we noted that when a stimulus was repeated more than 2 or 3 times the above mentioned responses tended to disappear.

In order to understand whether adaptation phenomena might occur at the same time both in the EEG and in the finger plethysmographic responses, 17 subjects were studied with a method reported by us elsewhere. A tone of fixed pitch, intensity and duration was presented to the sleeping subject every 20 sec. while continuous EEG, finger plethysmographic and respiratory records were taken. The stimulus was repeated 20 times and then no more.

The EEG and vasoconstrictor responses appeared fairly parallel for the first 2 or 3 stimuli but later showed considerable independence in that one response might appear without the other. If however both responses were present the delay of the vasoconstrictor response in relation to the K complex was constant (3-4 sec.).

The lack of appearance of the K complex following the stimulus was considered as possible evidence of adaptation, but conditioning phenomena to the fixed time interval soon commenced to appear. EEG changes indistinguishable from K complexes, often followed by vasoconstriction with the usual delay, began to appear just before the expected stimulus, particularly between the 8th and 11th repetition (anticipatory responses). EEG changes similar to the above often occurred after the series of 20 stimuli, at about the time when the 21st stimulus was due, though never given.

A common feature was that adaptation phenomena, as judged by the lack of response to a stimulus, did not usually last for more than 3 or 4 stimuli. The K complex and/or the vasoconstrictor response would then appear either following the stimulus (loss of adaptation), or just preceding it (anticipatory response), though there was no constant relationship between these phenomena. There were considerable variations between subjects, but the phenomena reported were observable whether sleep was spontaneous or induced by barbiturates.

6. An investigation of the suppressive effects of novel stimuli on a 4 to 5 c/sec. temporo-occipital discharge in the EEG of an adult woman. — A. L. Winter, Burden Neurological Institute, Bristol.

A woman, aged 46, was referred for EEG studies with a history of major attacks for the past 24 years. Eighteen months ago she had a right Bell's Palsy from which she subsequently recovered; there was no apparent connection between this latter ailment and the other features of her condition.

The records were complex; the principal component was a rhythmic 4 to 5 c/sec. temporo-occipital discharge which was not synchronous in the two hemispheres. It was noticed at once that the slow rhythms were suppressed for a short time by sudden noises, requests to shut the eyes and by opening the eyes. Trials were made to define the nature of the stimuli which were most effective as "alerting" agents. Any form of mental effort suppressed the slow rhythms at first but with repeated trials the effect wore off; it could be restored by reintroduction of a novel feature. The extent of the effect could be measured with the wave analyser and plotted on a suitable graph.

It is suggested that in this case the bilateral responsive slow rhythms may indicate the action of a mechanism capable of deriving a measure of "surprise".

7. The role of non-specific cortical projections in the structure of the EEG of psychomotor seizures. — Henri Gastaut and Micheline Vigouroux, Faculté de Médecine, Marseille, France.

The material was provided by observations and recordings of 500 psychomotor seizures occurring spontaneously, or following over ventilation, flicker light stimulation or injections of Cardiazol or Megimide. The subjects presented temporal foci between seizures. The data so obtained are considered by us as being valid, for both spontaneous and evoked seizures in the same subject were comparable: there were no differences due to the method of producing a seizure.

The results are remarkably complex for there exists an infinite variety of EEG appearances of such psychomotor seizures. However, they may divided roughly into the following groups:

localized discharges revealing a spike rhythm occupying the temporal region (anterior and central temporal electrodes) the occipital region (occipital electrodes, posterior temporal electrodes and accessory parietal electrodes).

diffuse discharges consisting of waves progressively lengthening or shortening, more or less generalized, over the two hemispheres but predominant in the fronto-temporal regions.

complex discharges containing a combination of localized and diffuse discharges either independent or in association with other forms and in this last case with or without fixed phase relationships.

All these discharges, which may be preceded by a localized or diffuse flattening, are remarkable for the length of their duration.

The interpretation of these data is based upon the anatomical, clinical and electrophysiological correlations which we have carried out for our cases and also depends on experimental comparisons:

the complex and long-lasting EEG appearances of psychomotor seizures depend upon discharges developing successively in different sectors of the brain and in different cortical projections (Erratic discharges, Gastaut and Roger 1953);

the amygdalo-temporal system is responsible for focal temporal discharges;

the diffuse thalamo-cortical system is responsible for diffuse discharges: (i) the centro-medial portion of this system is responsible for discharges predominating in the frontal regions; (ii) the postero-lateral portion is responsible for discharges predominating in the occipito-posterior temporal regions.

8. Spatial and temporal identification of alpha activities in relation to individual mental states, by means of the 22-channel helical scan toposcope. — R. Cooper, H. W. Shipton, J. Shipton, V. J. Walter and W. Grey Walter, Burden Neurological Institute, Bristol.

Technique

Frequency differences of 0.02 c/sec. in the alpha band have been resolved by the helical scan toposcope and use of 22 channels has enabled immediate visual auto-correlation and cross-correlation of rhythms from all parts of the head.

Good frequency discrimination in the presence of noise permits the use of wide band amplifiers (6 db down at 200 c/sec.) and rhythmic signals having signal/noise ratio 1:1 are easily discernible.

Correlation periods up to 10 sec. are used and the system has proved a useful complement to the Walter Analyser.

Selection of suitable scanning rates allows the study of frequency and spatial distribution of harmonics in the presence of the fundamental.

Observations

1. Resting records from normal show consistent individuality of alpha distribution and frequency within 0.05 c/sec. over periods of minutes, even when there is evidence of several alpha sources. In some individuals the frequency of an alpha source may change abruptly by as much as 0.5 c/sec.

2. The method is particularly suitable for studying the fine structure of the characteristic individual response to a variety of stimulus situations.

3. Illustrations will be given of these characteristics together with the influence of Meratran, LSD 25, and other drugs.

4. Use of the system with pattern flash stimulation facilitates distinction between spontaneous resting activity, spontaneous activity synchronised by specific stimuli and responses evoked by photic stimulation.

5. Experiments are in progress to test hypotheses relating the identity of alpha activities to specific physiological functions.

9. Awareness, consciousness, the brain stem reticular formation and the EEG. — S. L. Sherwood, National Institute for Medical Research, N.W.7. and Severalls Hospital, Colchester.

1. Awareness or consciousness can be impaired or abolished by more or less extensive or diffuse lesions in many parts of the brain, by equivalent chemical or pharmacological damage or by electric currents.

2. Similar but more critical effects can be observed if the same agents are employed by confining them to a minimal volume of brain tissue and at a strength a fraction of that used to produce such effects at a higher, i.e. more rostral level; in the case of lesions some sites in the diencephalon are particularly sensitive.

3. Appropriate experimental and clinical data show that in the case of a pre-existing experimental lesion or dysfunction, or in the case of clinical dysfunction, specific signs or symptoms may be reversed by agents affecting these sites.

4. A range of electrophysiological concomitants to these events is known from experimental work; although equivalent information in corresponding human clinical states is at present statistically insufficient, it is clear that the data available show similar trends.

5. The role of the brain stem reticular formation in relation to consciousness, awareness and related EEG findings is more complex and variable than that implied by "general activation", which occurs with somewhat gross means. In addition to our own data obtained from the intraventricular injections of drugs in animals and patients, the work of Starzl, Taylor and Magoun, of Sprague, and more recent work of Gellhorn and his associates, and of Ingvar and Söderberg shows that the nature of the influence of the brain stem reticular formation on behaviour can be subtle and specific. Hess' conclusions regarding these effects are that the brain produces ad hoc functional systems possibly involving a great number of structures within the brain which result in the complex reactions of a particular kind of behaviour.

6. What we are left with then is that the brain stem reticular formation as such has an important function as an integrator and an analyser of complex information. It is evident that time course, recovery cycles, thresholds and coincidences in this system are of utmost importance, for what we can observe with electrophysiological methods including the EEG is that the electrical disturbances consist of an alteration of interdependence between different regions of the brain; thus, transmission may fail on account of failure of conduction or inability of the ultimate structure to respond. Therefore, both blocked transmission and excess synchronization may interfere with the proper processing of signals and such failure may occur either over a wide area of nonspecific tissue or in a small area which holds control over a wide area.

10. Epilepsy and rheumatic fever. — Michael Jefferson, Queen Elizabeth Hospital, Birmingham.

The question of a possible link between epilepsy and rheumatic fever has attracted no attention in recent times, although it was discussed by physicians of the 19th Century. In the last 2 years, 4 patients have been seen complaining of fits, in whom an antecedent history of rheumatic fever was discovered, with clinical evidence of residual heart lesions. A fifth patient had a history of rheumatic chorea. In none of these cases were there grounds for regarding the fits as secondary to cardiac decompensation. The occurrence of fits and rheumatic illness in them is most probably a coincidental affair, but a direct aetiological link cannot be excluded *a priori*. It is conceivable that sometimes during the acute phase of rheumatic fever, rheumatic encephalitis (either manifest or subclinical) can produce lesions in the brain, which are capable of acting at a later date in an epileptogenic manner. The point can only be settled on a statistical basis.

11. Sleep EEGs in psychiatric patients. — Jean M. Nicholson and John R. Knott, Division of EEG, Department of Psychiatry State University of Iowa College of Medicine, Iowa, U.S.A.

Sleep recording was obtained in routine EEGs of 162 unselected psychiatric in-patients. Similar recording was obtained in 218 patients referred with a possible diagnosis of convulsive disorder, and 59 patients with other neurological disorders. The average ages of these groups were: 34 years, 28 years and 35

years, respectively. The youngest patient in each group was 12 years of age; a relatively greater proportion of cases between 12 and 20 years occurred in the convulsive group.

Temporal sharp or spike activity was seen in 10 per cent of the psychiatric group. Eleven per cent of the convulsive disorder suspect group, and in 10 per cent of the "other neurological disorder" group. The 14 and/or 6 per sec. positive spike pattern was seen in 20 per cent of psychiatric patients, in only 6 per cent of convulsive disorder suspects, and 9 per cent of "other neurological disorders".

The psychiatric group was broadly subdivided into those with: (1) *chronic brain disorders* (N = 23); (2) *psychotic disorders* (N = 93). The incidence of temporal sharp or spike activity was: 22 per cent, 11 per cent, and 7 per cent, respectively. The incidence of other sharp activity was: 4 per cent, 11 per cent and 3 per cent, respectively. Fourteen and/or 6 per sec. positive spike activity appeared in: 0 per cent, 15 per cent and 28 per cent, respectively.

The high incidence of the 14 and/or 6 per sec. positive spike pattern in the psychiatric group (especially the non-organic, non-psychotic patients, variously diagnosed as (*a*) psychophysiologic autonomic and visceral disorders; (*b*) psychoneurotic disorders; (*c*) personality disorders; and (*d*) transient situational personality disorders) would seem to warrant further exploration with particular reference to: (1) symptomatology related to the pattern; (2) etiological relationships of symptoms and EEG; (3) efficient avenues of therapeutic approach to psychiatric patients presenting 14 and 6 per sec. positive spikes in their EEGs.

THE WESTERN SOCIETY OF ELECTROENCEPHALOGRAPHY

La Playa Hotel, Carmel, Calif.

February 28 and March 1, 1957

Officers for 1957:

President: Dr. DONALD B. LINDSLEY

Vice-Pres.: Dr. S. N. BERENS

Sec.-Treas.: Dr. KENNETH BLINN

V. A. Hospital, Long Beach, Calif.

1. The theta rhythm as an index of frustration. — LEE EDWARD TRAVIS and EDDIE JOHNSON, University of Southern California, Los Angeles.

For this study two groups of children were used as the subjects; 33 young deaf children, and 33 matched aurally unimpaired children. Frustration was operationally defined as the snatching away of a candy sucker that the child had selected as his favorite sucker and upon which he was sucking at the moment of withdrawal. EEG data were secured under the condition of resting, sucking, frustration, and post-frustation. Theta waves were induced by frustation in all subjects. The deaf children gave theta waves for a very significantly longer period of time in the post-frustration period than did the normally hearing children. It was concluded that the theta rhythm is a valid measure of frustration tolerance in young children.

2. Effects of dietary treatment on the electroencephalogram in a case of phenylketonuria. — CHARLES L. YEAGER and JOHN I. LANGDELL, University of California School of Medicine and the State of California Department of Mental Hygiene, The Langley Porter Clinic.

Phenylketonuria is an inherited disorder of metabolism characterized clinically by mental retardation in association with the excretion of phenylpyruvic acid in the urine. Other clinical signs that might be present include fair hair, blue eyes, microcephaly, widely spaced incisor teeth, eczema, hyperreflexia, muscular rigidity, a flexed posture with short gait, hyperkinetic finger movements, generalized hyperactivity and convulsive seizures.

The inborn error of metabolism is determined by an autosomal recessive gene, resulting in an enzyme defect in the liver blocking the normal conversion of phenylalanine to tyrosine. As a result, high levels of phenylalanine and its metabolites accumulate in the body. On the premise that the mental disorder might be the result of toxic effects of these substances on the developing brain, diets low in phenylalanine have recently been employed in treatment. Reports of clinical improvement with dietary treatment support the hypothesis that the mental defect is a result of the metabolic disturbance and can be treated by biochemical means.

We have observed electroencephalographic and clinical signs of improvement in a 2 year-old phenylketonuric boy during treatment with a restricted phenylalanine diet.

The diagnosis was established at the age of 16 months by finding phenylpyruvic acid in his urine. A low phenylalanine diet was started at age 19 months, and a month later his EEG showed quantitative improvement on comparison with two electroencephalograms obtained before treatment. The original records showed a severely dysrhythmic, paroxysmal, slow record with spikes and domes and no normal basic rhythm, which meets the description of the severe, persistent spike and wave activity in children known as hypsarhythmia. After a month on the diet, the record showed the spike and wave activity to be noticeably reduced and occurring in short chains with relatively normal areas interposed. Three subsequent EEG's during dietary treatment have shown sustained improvement over the pre-diet records.

There has been clinical improvement in the form of a change from a lethargic, unresponsive child who seemed deaf and blind to an alert, smiling boy who obviously can see and hear. While he was unable to sit without support before treatment, he is now able to sit up. A tendency to ankle clonus and a Babinski sign also disappeared.

Biochemical, genetic, and electroencephalographic studies of other members of the family are under way. The mother's electroencephalogram has shown paroxysmal dysrhythmia of a non-specific type and of moderate degree.

3. Some technical notes on monopolar and bipolar recording. — G. L. MOWERY and A. E. BENNETT, Herrick Memorial Hospital Electroencephalographic Department and the A. E. Bennett Neuropsychiatric Research Foundation, Berkeley, Calif.

Four factors of the monopolar and bipolar techniques, inadequately treated in the literature, are not thoroughly understood.

I. The reason for reduced amplitude in the electroencephalogram when recording between closely spaced electrodes.

The amplitude changes that occur as the distance between the two recording electrodes is varied are not solely due to the distance factor, but to (1) the voltage of the electrical activity over each area and (2) the phase relationship between the electrical activity being recorded from each area.

II. The effect of ear electrode resistance in monopolar recording.

Some instruments use a switch to tie the ear electrodes together, and both ears are then used as a common reference point. But the resistance of the electrode contact of both ears is usually not equal. The instrument, even though set to record from both, records mainly from the ear with the lowest resistance, especially if the electrodes are attached by paste. This results in a decrease in amplitude of the recording over the temporal lobe on the side of low resistance ear contact.

III. A low mid occipital electrode used as a reference.

In certain cases of low temporal lobe lesions or psychomotor epilepsy, a generalized abnormal pattern can be avoided and the pattern correctly interpreted by using a centrally located common reference point such as the low mid occipital area to check the amount of electrical activity at the ear. This reference point is of most value during the drowsy phase of sleep when the alpha rhythm has dropped out.

IV. The effect on the EEG of using an active ear electrode as a reference.

If, in cases of temporal lobe epilepsy, a negative spike discharge occurs at the ear lobe that is used as a common reference, a positive deflection will be recorded from all channels except from the focal area where a negative deflection appears although reduced in amplitude. Three further questions regarding the reasons for the direction of pen deflection are raised.

Recording between closely spaced electrodes or using an active ear reference electrode must therefore be done with caution. In order to avoid complete cancellation of abnormality over the temporal lobe, several different common reference points such as the low mid occipital, vertex, ears or average reference point should be used at the beginning of the recording.

4. Some clinical correlation of 14 and 6 per sec. spiking activity. — RICHARD D. WALTER, University of California, Los Angeles.

Positive spiking at a repetitive rate of 14 and 6 per sec. has been reported as an abnormal finding in some children with a variety of clinical states ranging from gross central nervous system disease to behavior disorders. The neurophysiology of this finding remains speculative and little is known concerning its development. The onset and appearance of 14 and 6 per sec. spiking activity was studied in one case, following known central nervous system anoxia. After an anesthetic accident the patient remained comatose for 24 hours. Her neurological findings gradually improved over a period of weeks, during which time serial recordings revealed the onset of 14 and 6 per sec. activity. The clinical status of 20 cases in which this electrical finding has been observed fails to reveal any single, common, characteristic.

5. The electroencephalogram in forensic (criminology) alcoholism. — A. A. MARINACCI, University of Southern California, Los Angeles.

This report is limited to the EEG's of patients with the history that alcohol was alleged to be the exciting cause of convulsive seizure, altered consciousness, a fugue state, abnormal rage, a "blackout" or automatism (psychomotor epilepsy) which resulted in automotive manslaughter, use of firearms with fatal results, robbery or other antisocial acts. Because this is a sporadic occurrence, the routine brain wave is usually normal. It was thought that giving a specified dose of alcohol as a test following the routine brain wave might bring out some latent abnormal epileptic discharges. It would therefore be possible to express an opinion with reasonable medical certainty that alcohol was responsible for the altered state of consciousness in such an individual. The criminal or antisocial act was likewise a result of a minor degree of alcoholism.

Materials. — Sixty-nine individuals who claimed that alcohol altered their consciousness with consequent antisocial acts were studied in this series. A routine EEG was taken first and was then followed by an EEG after administration of alcohol by mouth.

Of the 69 patients, 13 showed electrical seizure discharges after the administration of alcohol.

It is pertinent to point out the legal significance of this picture for any such episodes that had resulted in manslaughter, fatal shooting or other antisocial behavior. In a large majority of the cases, in addition to the clarification of the clinical diagnosis, the electroencephalographic study was called upon to answer the question: "Was this patient suffering from an epileptic seizure or from some other abnormal cerebral state which rendered him unconscious of his environment, making his acts automatic and without volition, thereby depriving him of reason so that he was unaware of the wrongfulness of his acts and unable to comprehend the nature and the quality of his acts?". In order to answer such a question in the affirmative, the electroencephalograms had to be definitely abnormal after ingestion of alcohol.

General considerations. — There is the possibility that in some individuals the ingestion of alcohol lowers the convulsive threshold to a degree which varies between a few subclinical electrical seizure discharges on one hand to actual convulsive spasms on the other. The following factors must be taken into consideration in the evaluation of each case:

(1) The post-alcohol tracings were made over a longer period than the routine EEG's.

(2) Coincidence must also be considered as a possibility.

(3) Sensitivity to alcohol as well as toxicity from contaminants in the alcoholic beverage such as woodworm oil may have affected the findings somewhat.

We find therefore that a predisposition to abnormal cerebral states as well as other factors appear to be involved in bringing out clinical seizures whether it may be one, two or three in the lifetime of the individual.

Conclusion. — One should not conclude that every person who drinks alcohol has epileptic seizures nor that alcohol is the only cause of an isolated seizure

for isolated epileptic seizures may be observed under many circumstances. The writer does not recommend the use of alcohol as an activator of potential dysrhythmia. It should be used only in specific cases in which the alcohol is alleged to be the cause of some antisocial act.

6. The EEG effects of intracarotid Hypaque. — Eldon L. Foltz, Lawrence M. Knopp and Richard P. Schmidt, University of Washington, Seattle.

The electroencephalographic effects of 50 per cent Hypaque sodium injected into the carotid artery on one side has been studied in a series of 12 patients. The pre-injection EEG studies showed that 3 cases had delta foci secondary to tumor, 3 cases had delta foci secondary to vascular disease, 3 cases had spikes or sharp wave activity from cerebral cicatrix, and 3 cases were essentially normal EEG. In all instances, the patients were suffering from definite neurological disease, and none were considered clinically normal in spite of a normal EEG.

The Hypaque injections were done in the manner identical to the injections of cerebral arteriography, except that the EEG was running continuously with adequate controls before injection, after the needle was in place in the artery, during and following injection of the Hypaque, and during and following injection of equal amounts of control solutions.

The clinical safety of Hypaque as a cerebral angiographic contrast medium is supported by the relatively benign changes induced in the EEG by the intracarotid Hypaque. These changes are presented and discussed in light of the effect of Hypaque on the basic EEG activity in each group of cases. The effects of the injections on the pulse rate and respirations are likewise recorded and discussed.

7. Further electroencephalographic correlations between pathological intoxication and psychomotor epilepsy. — George N. Thompson, Los Angeles.

Further evidence for the relationship between pathological intoxication and psychopathic personality is seen in some cases of psychomotor epilepsy. The evidence, particularly electroencephalographic, points to the fact that the disorders are essentially identical. This interesting association of some cases of psychopathic personality with psychomotor epilepsy and pathologic alcoholic intoxication indicates that pathologic alcoholic intoxication and psychomotor epilepsy may be the same disease under two different names. In the one case (psychomotor epilepsy) psychomotor epileptic attacks simply occur spontaneously; in the other (pathological intoxication), psychomotor attacks occur under the stimulus of alcohol. A number of patients with sexual psychopathy behave as is they had psychomotor attacks. As a matter of fact, there have been patients who have engaged in extremely bizarre psychopathic behavior and later had no recollection of it; these cases are so similar to cases of psychomotor epilepsy that there is essentially no clinical differentiation. However, it is only some cases of sexual psychopathy that fit this pattern.

THE EASTERN ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

Ste. Adèle, Quebec, Canada

March 1, 1957

Secretary: Dr. JOHN W. SCOTT

Toronto General Hospital, Toronto 2, Ont., Canada

1. The effect of positive acceleration with hyperventilation on the EEG. — H. P. Brent, T. J. Powell and J. W. Scott, RCAF Institute of Aviation Medicine, Toronto, Canada.

Unexplained periods of brief unconsciousness, occurring in RCAF jet aircrew during flight, have been under investigation at the Institute of Aviation Medicine, Toronto. Circumstances surrounding these incidents are subjected to a close scrutiny and the airman is examined medically, and subjected to stresses similar to those encountered in flight.

During these investigation routine EEG's are recorded under conditions of rest, during hyperventilation, during positive acceleration and during a combination of hyperventilation and positive acceleration. These studies are made in both the fasting and the post prandial state. Samples for blood sugar determinations were obtained at the time of each test. The routine was arranged so that hyperventilation was not repeated in less than an hour to avoid any possible cumulative effects.

At first serious technical difficulties were encountered since the EEG cable was over 60 feet long, and interrupted by a commutator ring.

The results indicate that the EEG is more stable in the post prandial than in the fasting state. Some men show no slow activity with hyperventilation alone, but when subjected to hyperventilation combined with positive acceleration, slow waves are induced. Others who show slow waves with hyperventilation will show them much more rapidly when subjected to positive acceleration.

It is concluded that the stresses produced by hyperventilation and positive acceleration are additive, and combined may be sufficient to interfere with cerebral function, while either stress alone has no demonstrable effect.

2. The pattern of inheritance of cerebral light sensitivity. — C. Wesley Watson and Sherwood Davidson, Boston, Mass.

In certain individuals, otherwise well, many affected by chronically recurring seizures, and among their relatives there was evoked by flickered light falling on the retina an unusual cerebral electrical change the characteristics of which were defined. Such individuals and relatives were termed "light sensitive".

An analysis of the pedigrees of 43 families comprising 155 tested individuals revealed: 1. 62 per cent of the families had one or more light sensitive relatives other than the propositus. 2. Penetrance within a family was high, if variable, with up to 100 per cent

of a sibship of four affected. 3. Three consecutive generations were affected. 4. The trait affected males and females equally. 5. The trait was not sex-linked. 6. Presence of the trait was independent of a commonly shared environment.

Defined cerebral electrical changes evoked by flickering light occurred in 36 per cent of 112 relatives (only) of 43 propositi but in only 2 per cent of a control series of 100 individuals, indicating both the abnormal and familial characteristics of the condition of which the evoked cerebral electrical changes were a manifestation. The hereditary character of the trait was demonstrated by the distribution within the pedigrees.

3. Reflections on the spike and wave complex in cortical and centrencephalic seizures. — HERBERT H. JASPER, Montreal, Canada.

The physiology and functional anatomy of the spike and wave complex remains poorly understood despite extensive investigation. Much confusion has arisen from the identification of the electrical pattern itself with petit mal epilepsy; as it may be seen also in focal cortical seizures. The spike and wave is always a cortical potential complex and may be more less determined by functional properties within the cortex itself. However, there is no known mechanism to explain how otherwise normal cerebral cortex in frontal and parietal areas of both hemispheres can suddenly and simultaneously be made to give rise to such a regular rhythmic discharge, symmetrical from the two hemispheres, if it were to be of uniquely cortical origin. Seizures of known cortical origin do not behave in this manner. The more closely interconnected network of neurones in the thalamus and brain stem, with diffuse bilateral projections especially marked in frontal and parietal cortex, seems most probably involved in the mechanism of the petit mal attack, and probably also in its origin, since this mechanism is capable of the sudden reversible effects upon consciousness which characterize these seizures.

Cortifugal projections producing secondary bilateral synchrony, especially from parasaggital and orbital frontal regions, are of major importance in some cases. Transcortical and commisural connections are of importance in the ''synchronization'' of epileptic discharges simulating the petit mal form (slow spike and wave, etc.) in patients with extensive diffuse bilateral cortical epileptogenic lesions, but this is not petit mal epilepsy.

4. A combination of EEG findings which correlate with psychiatric disturbances. — ERNST A. RODIN, Ann Arbor, Mich.

It is well known that patients who have electroencephalographically marked focal abnormalities in one or both temporal areas have frequently, in addition to ''temporal lobe'' seizures, severe interictal psychiatric disturbances. On basis of the focal EEG findings alone one can not predict at the present time whether the patient's personality structure is likely to be intact or severely interfered with. It was observed that there exists a group of patients who have, in addition to the marked focal changes in their EEG's a diffuse slowing of the background rhythms. The alpha rhythm is in these instances largely replaced by medium voltage 5-7 c/sec. activity. Eleven patients were observed during the period of November 1, 1955 to October 31, 1956 who met the mentioned criteria in their EEG's. All of them showed clinically marked psychiatric disturbances. As a control study all EEG's which had been obtained during the year of 1951 in this laboratory were screened for the mentioned syndrome without knowledge of the clinical condition of the patients. Twelve records were found which fit into the described category. Subsequent review of the clinical charts on these patients showed findings which were quite similar to the group of patients seen during the year 1955-56. The findings will be discussed in detail as well as their possible etiologies and their significance for the electroencephalographer.

5. Sphenoidal electrodes: An effort toward their popularization. — CURTIS MARSHALL, Baltimore, Md.

A simplified technique is presented which should make these basal electrodes readily available in all clinical laboratories of electroencephalography. Standard sterile non-insulated i.v. needles are used with single strands of sterile insulated wire to obtain artifact free precise identification and localization of the electrical activity of the inferior aspect of the temporal lobes.

6. The electroencephalogram in subacute inclusion encephalitis. — GILBERT H. GLASER, Yale University School of Medicine, New Haven, Conn.

Electroencephalograms are described of two middle-aged women (ages 56 and 57) with pathologically verified subacute inclusion encephalitis. Both had similar clinical pictures manifested by progressive organic mental deterioration but not seizures. The EEG of each was characterized by diffuse theta and delta waves mainly from the frontal and temporal regions, with a unilateral preponderance, correlated in one instance with focal neurological symptoms. Both recordings also contained periodic episodes of high voltage 2-4 c/sec. waves appearing synchronously from all areas, recurring every several seconds, and in one case having the appearance of repetitive complexes. The development of these periodic discharges is shown during a ten day period associated with rapid mental deterioration.

The EEG alterations are similar to those previously reported as being specifically characteristic for subacute progressive encephalitis with or without inclusions. These earlier cases were in children and adolescents, and almost all had seizures. The present cases indicate the occurrence of the disease and EEG phenomena in the middle-aged, correlated more with the intensity of diffuse cerebral dysfunction with dementia and not seizures. The EEG abnormalities are probably non-specific since they appear in a variety of diffuse encephalopathies especially of metabolic and encephalitic origins.

7. The lack of necessity for sleep in the EEG or ECG diagnosis of temporal seizures. — P. GLOOR, C. TSAI, F. HADDAD and H. H. JASPER, Montreal, Canada.

The EEG records of 189 patients who underwent temporal lobectomy for seizures in the years from 1939-1956 were analysed. The pre-operative EEGs in these patients were reviewed and the effectiveness of sleep and wake records compared in all cases in which sleep was recorded. In 163 out of these 189 patients the EEG diagnosis was made without necessity to resort to a sleep record. This represents 86.2 per cent of the total number of cases. In only 11 of these patients Metrazol activation was necessary to arrive

were encountered in 10 patients (6 of whom had fast activity induced in their EEG's) and to a lesser degree in 12 other patients. Comparative figures and illustrative tracings will be presented. It was concluded that Placidyl is a safe and effective sleep-inducing for in-patient use, but that because of the possibility of distressing subjective symptoms upon early arousal, Dormison is preferable for out-patients.

12. Clinical and EEG evidences of cycloserine activity on the central nervous system. — Lewis L. Levy, West Haven, Conn.

Clinical observation and serial EEG examination of 24 patients, during the course of treatment for pulmonary tuberculosis with cycloserine, has been carried on for the past two years. The drug previously reported to cause convulsions in humans, caused seizures in 8 of the 24 patients. A total of 16 patients reported toxic symptoms referable to the CNS; lethargy, dizziness, ataxia, behavioral disorder. In 13 of the 24 series of EEG examinations there was change from alpha rhythm to slowing of alpha, or theta and delta frequencies. There was no clear association of EEG change to clinical symptoms.

An additional group of 7 patients previously followed after cerebral infarction were given cycloserine for three to five days. In these cases delta foci were reproduced without significant change in the neurologic status of the patients.

13. EEG changes during prolonged administration of low, graded concentration of ether. — Harry A. Kaplan, Benton D. King and Stanley W. Weitzner, Brooklyn, N.Y.

Investigations were undertaken to study the EEG and the behavior patterns resulting from the administration of low, graded, concentrations of ether. Continuous electroencephalographic recordings, simple psychological assessment, and gross sensory testing were utilized for evaluation. Ten patients were given slowly increasing, and then slowly decreasing precisely-graded concentrations of ether over a period of several hours. The general pattern of the electroencephalogram in most of the cases showed progressively the following changes as the ether concentration was being increased: (1) a dropping out of alpha waves; (2) an increase of slow activity; (3) a lowering of the voltage; (4) an appearance of beta waves; (5) an increase in the number of slow waves with a dropping out of beta waves. High voltage slow waves appeared with the development of surgical anesthesia. As the ether concentration was decreased, the electroencephalogram returned to the pre-ether pattern in the reverse of the order stated above. There were no constant correlations between electroencephalogram pattern and behavioral response and the non-anesthetic concentrations of ether employed in the study.

14. Cortical D. C. changes accompanying recruiting responses. — Sidney Goldring and James L. O'Learey, St. Louis, Mo.

Observations were made in cat and rabbit, with attempt to control the anesthesia factor as far as possible. The midline nuclei of the thalamus were stimulated with bipolar electrodes, with transcortical recording (surface-reference) from the anterior frontal cortex of the rabbit and the anterior suprasylvian gyrus and gyrus proreus in the cat. Stimulating and recording electrodes were positioned to obtain a surface negative recruiting response upon repetitive stimulation. A potentiometer in series with the animal and amplifier was used to balance the steady potential (SP) across the cortex, permitting monitoring of change in baseline with a convention electroencephalograph short-circuited 8 times per second. Quick transients, single or recruited, activated by stimulation and the accompanying D.C. changes were also recorded upon an oscilloscope operating from a D.C. amplifier.

In the lightly etherized rabbit a single response is followed by a negative after-effect which lasts 0.3 to 0.4 sec. With repetitive stimulation, each volley lasting one second, the after-effects summate with the result that the baseline shifts negatively during the period of stimulation and the negativity outlasts the latter for a longer period than the duration of a single after-effect. Increase in stimulus frequency 2/sec. to 100/sec. progressively increases the amplitude of the baseline shift and the persistence of the post-stimulatory disturbance. With brief periods of stimulation at 100/sec. the negative shift amounts to 500-700 μV. and returns to the pre-stimulatory level 3-5 sec. after cessation of the stimulus. During after-negatively excitability as measured by recruiting response amplitude is reduced. With longer stimulation (10-15 sec.) the negativity falls off during stimulation and the baseline may even shift positively for 5-15 sec. During this positive shift excitability is also reduced. Occasionally with prolonged supramaximal stimulation, cortical paroxysm is initiated which outlasts the period of stimulation. During such paroxysm SP remains negative, shifting positively with the termination of high-voltage synchronized discharge. This differs from the events ordinarily seen in recording from a cortical projection area during repetitive stimulation of the related thalamic relay nucleus. Results are essentially the same in anesthetized and unanesthetized preparations.

In the cat, the slow potential phenomena are similar in general but differ in detail. Following a single stimulus in the decerebrate cat, the response is diphasic (negative/lower amplitude positive). When recorded with a D.C. amplifier the positive phase is observed to last 0.2 to 0.3 sec. A second response evoked during this positivity recruits, as does a second response during the negative after-effect in the case of the rabbit. With repetitive stimulation the baseline shift is negative at frequencies from 20-100 sec. and occasionally so at 15-20/sec. Below 15/sec. either no shift occurs or the shift is positive, with return to prestimulatory level within 0.1 to 0.2 msec. With ether anesthesia both negative and positive phases are reduced in amplitude but the positive phase is affected the more. Further the SP commences to shift negatively with stimulation at lower frequencies (10-15/sec.). Overall, with repetitive stimuli to the midline thalamus a negative shift is more readily produced in rabbit than in cat.

15. Microelectrode studies of thalamic afferents to pyramidal cells of the motor cortex of the cat. — A. R. Martin and Charles L. Branch, Montreal, Canada.

Capillary glass microelectrodes have been used to record from single cells in the sensory-motor cortex of the cat. The investigation is limited to those cells whose axons lie within the pyramidal tract. This is determined by stimulating the pyramidal tract on the ventral surface of the medulla about 5 mm. caudal to the pons, and looking for antidromic responses in the cortical units. Stimulating electrodes were also

placed in the nucleus ventralis lateralis (V.L.) of the thalamus. A study was then made of the effect of this stimulus on the cortical cells.

Almost all cells studied were spontaneously active. Their response to single shocks applied to V.L. was usually intermittent and action potentials, when they occurred, had latencies ranging from 0.5 to 30 msec. Likewise, response to repetitive stimulation of V.L. was highly variable. However, repetitive stimulation was always accompanied by a cessation of the spontaneous activity, which remained suppressed for several seconds after stimulation had ceased. The duration of this silent period could be increased by increasing the frequency of stimulation, the optimum frequency being about 30/sec. Increasing the duration of the repetitive stimulation usually had only a small effect on the length of the silent period.

It is unlikely that the cessation of spontaneous activity was due to inhibition or fatigue of the pyramidal cell itself because: (1) repetitive antidromic stimulation did not interfere with spontaneous activity and (2) the cell remained excitable antidromically during the silent period which followed stimulation of V.L. Responses to V.L. stimulation could also be obtained during the silent period, showing that the pathway from the thalamic nucleus to the pyramidal cell was intact.

It is concluded that stimulation of V.L., as well as exciting the pyramidal cells, has a specific inhibitory effect on other cells involved in the spontaneous activity. The location of these cells is not as yet known, but records have been obtained from the sensory-motor cortex which show intracellular inhibitory potentials following V.L. stimulation, in cells which are not excited antidromically by stimulation of the pyramidal tract.

16. Blood pressure alterations secondary to amygdaloid seizures. — O. J. Andy, R. McC. Chinn and P. Bonn, Jackson, Miss.

In a series of 30 unanesthetized cats, seizures were induced in the amygdala and its environs. Blood pressure and electroencephalographic recordings were made simultaneously. Cortical and subcortical electrodes were placed under local anesthesia. After-discharges were induced with electrical stimuli: 1 msec. pulse, 30 sec. frequency, for 5 sec. at 1½ to 5 V.

In over 90 per cent of the stimulations, there was a definite drop in the blood pressure which in most instances was between 20 to 35 mm.Hg. The depression occurred with onset of stimulation and reached its maximum within 5 to 21 sec. after stimulation. In some instances a double dip occurred. The second of the two depressions was usually greater than the first. This change was found to correlate with the longer seizures. Pulse rate did not change appreciably during the after-discharge. However, there occasionally was a decrease in pulse pressure which was at the expense of its diastolic value. In one experiment there were very definite rises in blood pressure near the termination of the seizures. It is of interest to note that the seizures of shorter duration (less than 10 sec.) had a tendency to produce a 5 to 10 mm. greater drop in blood pressure than seizures of long duration (over 10 sec.).

17. Diurnal variation in periorbitally measured eye potential level. — Christine Kris, Cambridge, Mass.

Measurement of periorbitally recorded eye potentials for the simultaneous study of diurnal variations in physiological state, and of oculo-motor performance in response to visual stimulation, is demonstrated and its application to the study of alertness and sensory-motor responsiveness measured in terms of variations in precision and regularity of eye movement during successive target fixation and visual search, during different states of wakefulness is discussed.

Eye-potential changes corresponding in size and sign to direction and distance between given pairs of points in an electrically controlled hemispherical visual field, are binocularly measured by means of bipolar pick-up from two pairs of non-polarisable surface electrodes placed equidistantly from each cornea, above-below, and laterally-mesially about each orbit. Vertical and horizontal eye motion components are separately and simultaneously recorded on 4 d-c and 4 a-c channels. The relation between voltage changes obtained from eye position changes corresponding to controlled fixation shifts is evaluated with reference to potential level, which is defined as the size of potential change recorded during a standard (''eye calibration'') 60° fixation shift.

Size of potentials between electrodes has been found to remain nearly linear with respect to angular magnitudes of optic axis rotation ranging from $< 5°$ to $> 60°$ in the horizontal, vertical and diagonal directions for test of up to 2½ hours, when physiological and environmental conditions are not markedly varied. However, the constant of proportionality (i.e. slope of the curve of potential against visual angle) changes with the individual's diurnal sleeping-waking pattern of responsiveness, and also with other induced physiological and environmental (eg: illumination) alterations.

Characteristic patterns of variation over the diurnal period and indicative of physiological condition have been found to occur in potential level (— in the early morning hours, immediately after deep sleep, potential level is about that of the day peak). Related, but at present less predictable fluctuations include: (*a*) velocity of eye motion, (*b*) precision and regularity of target fixation (eg: overshooting and missing), (*c*) blink rate, (*d*) binocular coordination as contrasted to asymmetry, and (*e*) liminal illumination threshold.

A regular pattern of change in ''eye calibration potential'' accompanying the process of light adaptation (and which resembles a damped oscillation lasting approximately one hour, with high peaks at ten and thirty-five minutes) remains almost constant in shape and timing, but varies considerably in amplitude (*a*) with time of day, and (*b*) with level of illumination. A shorter, single peaked dark adaptation pattern has also been found.

A comparison of the efficacy of d-c versus a-c recording of eye position and of rate and distance of fixation shift can be obtained by inspection and by analysis of the data presented.

PRINTED IN CANADA

BOOK REVIEWS

Edited by CHARLES E. HENRY

PSYCHO-SURGERY AND MENTAL FUNCTIONS

J. LE BEAU

Masson & Cie, Paris 1954. One vol. 16 x 24 cm., 429 pp., 8 fig.,
39 tables, 2 coloured plates.

Workers in neurophysiology must surely find this book of interest, representing as it does a most careful analysis of experimental facts gathered by a neurosurgeon, aided by a team of specialists in all pertinent branches.

The reader will find the book well-organized and profusely illustrated. It contains many original findings on the correlation between cerebral function on the one hand, and either the anatomy or the physiology (as investigated by surgery) on the other. These findings are given not only from the clinical point of view, but also from the psychological and electro-physiological as well.

The book is divided into four parts of rather unequal importance:

The first part of the book is an excellent condensed inventory and critical review of the present knowledge of the anatomy and physiology, principally of the frontal lobes, but also of the temporal lobes and the brain stem. In parallel with this inventory are classified the known clinical and psychological facts concerning neuroses and psychoses, as well as intractable pain.

The second part is devoted to the treatment of mental disorders by psychosurgery, and will be especially of interest to the neurosurgeon and neurologist. The technique of the classical operations is described in three groups: operations on the frontal areas (leucotomies, sub-cortical sections, topectomies, sub-orbital resections, cingulectomies), operations on the temporal areas, and operations on the brain stem. At the end of the second part there is a most careful study of complications: their causative factors, their chronology, and their treatment, followed by a chapter on the readaptation and re-education of patients who have undergone these operations.

The third part — the most important, since half of the book is devoted to it — considers the results. Its first chapter treats the effect of lobotomies on psychoses, neuroses, and intractable pain. The next four chapters analyze very minutely the effect of ''selective frontal surgery'' on mental disorders and intractable pain. The results of different operative localizations are compared, and the indications for selective surgery are systematically given''.

In two succeeding chapters, the results are reported for operations on the temporal regions, the diencephalon, and the mesencephalon, for mental illnesses, intractable pain, and for other purposes.

The fourth and last part, which is titled ''Research on the functioning of the frontal lobes'', considers successively the knowledge gained from observations of the post-operative syndrome, and that gained by extensive pre-and post-operative psychological interpretation of the anatomical-physiological relations of mental illnesses, the mode of action of psycho-surgery, and some mental and physical correlations.

This remarkable work is closed by some general conclusions, a bibliography of about 350 references (English, German, Spanish and French), and an index.

The book is based principally on the careful study of about 175 patients followed over the course of a number of years. Fifteen selected cases are given in particularly complete detail, and well illustrate the various types of operations.

Le Beau extensively develops and defends his thesis of ''Selective Frontal Surgery''. He has been able to establish the existence of a certain number of anatomo-clinical syndromes by clinical observation and the extensive, intelligent use of specially adapted psychological tests of the type proposed by Eysenck, as applied to a wide variety of neurotic and psychotic patients. The modification in personality produced by operations in various regions of the frontal lobes gives the best indication of the preferred type of operation in certain clinical syndromes. The seven best-defined syndromes are the following: resection of the dorsal convexity of the frontal lobe produces a combination of indifference, euphoria, and of instability without anxiety. A section more anteriorly produces an affective indifference without anxiety. Sectioning of the anterior orbital surface is followed by a considerable inertia, and also by notable physical reactions to all stimuli. It produced also euphoria without excitation. Posterior orbital sections are accompanied by an extreme inertia, requiring feeding of the patient. Cingulectomies by contrast have a calming effect with a minimum of

irritation and agitation. Sectioning of the frontal pole, when not followed by diverse complications, produce rather an euphoria with a melange of excitation and indifference. Finally, operations on the internal surface of the frontal lobes partake somewhat of the syndrome of the base or of the convexity when one of these is touched by the section, and is accompanied by inertia or hypomania.

Thus, thanks to the isolation of these seven syndromes, one should be able to apply the selective operative procedure to various psychological deviations, without danger of lowering intellectual ability. It may be noted especially that the operations on the convexity reduce neuroticism and introversion without modifying the psyche. The cingulectomies affect at the same time the neuroses and psychoses and do not modify the equilibrium between extra- and introversion. Interventions on the internal surface should have an intermediary indication.

With "Psychosurgery and Mental Function" Le Beau has given the medical literature a classic of great value. The electroencephalographer can only regret that the team of specialists aiding Le Beau was initially formed when EEG was not yet a routine procedure in the hospital of Paris.

Considering the important place psychology now occupies, the precision of the clinical observations and the spectacular experimental approach to the problems of neurosurgery should make this book of importance to all interested in the neurological sciences.

A. RÉMOND

WANTED

Opening for trained EEG technician in established laboratory of private clinic in Southwest. Salary open. May limit to half time if desired, or combine with other laboratory or research activity. Cultural and recreational advantages. Excellent clinical material. Contact Arthur Arnold, M.D., Lovelace Clinic, Alburquerque, New Mexico.

FOR SALE

Offner Type C Four-Channel EEG, eight years old. Electronically in good shape, cabinet only fair. Switching to new larger machine ourselves. Any reasonable offer considered — guarantee if desired. May be inspected. Paper and spare parts available if desired. Please reply to: THE EEG JOURNAL, 3801 University Street, Montreal, Canada.

PRINTED IN CANADA

THE ORGANIZATION OF THE CEREBRAL CORTEX

D. A. SHOLL

Methuen and Co. Ltd., London, and John Wiley and Sons Inc., New York, 1956,
xvi + 125 pp., 12 plates, $4.25.

This is another of a recent series of small books which attempt to throw light on the manner of functioning of the cerebral cortex. Of the others one might mention Bonin (*Essay on the Cerebral Cortex*), Ashby (*Design for a Brain*) and Walter (*The Living Brain*). In the present volume an attempt is made to determine the possibilities of a statistical approach in terms of probability theory. This attempt is made necessary by despair of comprehending, in the predictable future, the intricate details of cortical structure.

The author begins by reviewing the anatomical methods used to study the cortex, detailing their deficiencies. Although an enormous amount of information has been accumulated, it has not resulted in any clear conception of the mode of functioning. There is nothing to be gained by trying to summarize these chapters. The author's account is already too condensed. As he says himself, it has been necessary to choose and this necessity results in injustice to some methods, for example, the method of strychnine neuronography. The author establishes his main point, however, which is that however unfruitful these anatomical studies have been for our understanding of the mode of operation of the cerebral cortex, an immense amount of accurate information has been accumulated and no theory which attempts to account for its activity can be in contradiction with these anatomical details.

The author then examine the attempts to apply quantitative methods to the cortex. He is equally critical of the deficiencies of these methods. He notes that they are tedious and often accumulate data which are of little interest because they do not bear on any obscurity which it is desirable to clear up. He notes that the difficulties are formidable and that, for many of the problems, no useful solution has so far been found. The margin of error is uncomfortably great so that the results of such a simple attempt as that of counting the numbers of neurones in the cortex gives figures which range from 1.2×10^9 to 1.4×10^{10}.

In discussing the experimental studies of the Pavlov school, the author dismisses them briefly for two reasons: first, the rather childish theory on the basis of which Pavlov tried to explain the results; and second, on the ground that conditioned reflexes can be established in the absence of the cortex. It should be pointed out, however, that the second argument is illogical. It does not prove at all that conditioned reflexes are not normally established in the cerebral cortex; moreover this is all the more certain since, in the absence of the cortex, conditioned reflexes can be established only imperfectly and with great difficulty. However childish Pavlov's theory may be, any theory which purports to account for the activity of the cerebral cortex may not ignore or contradict the vast amount of factual data which the school of Pavlov has accumulated.

Again, when the author discusses the results of lesions of the cortex in man he tends to simplify his problem and does not mention large parts of the parietal and temporal cortex where lesions produce constellations of symptoms well known to neurologists, such as the aphasic syndromes, Gerstmann's syndrome, Arnold's syndrome and the like. These are all the more disconcerting because they tend to result from lesions of the left hemisphere in right-handed people although the corresponding areas of the right cortex have the same structure and, so far as we know, the same connections.

However that may be, the author discusses the various theories which have been proposed in modern times by Lashley, Pavlov, Hebb, Ashby, Walter and others and notes their inadequacies. He then discusses the mathematical theories, in which he is primarily interested, of Wald, Pitts and McCulloch, Cragg and Temperley, Sholl and Uttley, Beurle and others and admits that they are all highly speculative, but concludes that "any theory which attempts to account for the properties of the dynamic spatio-temporal system that forms the basis of our behaviour must employ statistical hypotheses".

This small book can be warmly recommended as an introduction to those interested in the modern attempts to apply quantitive methods to the study of the cerebral cortex.

PERCIVAL BAILEY, M.D.

PRINTED IN CANADA

Supplement No. 6

CONDITIONNEMENT ET RÉACTIVITÉ EN ÉLECTROENCÉPHALOGRAPHIE

(The fifth colloquium of Marseille, 1955)

475 pages, price $15.00

Edited by H. FISCHGOLD and H. GASTAUT

Foreword by W. GREY WALTER, Introduction by A. FESSARD

Rousinov, V. S. et Smirnov, G. D. (Moscou).

Quelques données sur l'étude électroencéphalographique de l'activité nerveuse supérieure.

Jus, A. et Jus, C. (Varsovie).

Les méthodes bioélectriques dans l'expérience conditionnelle clinique.

Jouvet, M. et Hernandez-Peon, R. (Los Angeles).

Mécanismes neurophysiologiques concernant l'habituation, l'attention et le conditionnement.

Morrell, F. (Minneapolis).

Effets de lésions épileptiques focales sur la formation de connexions temporaires chez le singe.

Yoshii, N. (Osaka).

Principes méthodologiques de l'investigation électroencéphalographique du comportement conditionné.

Buser, P. et Borenstein, P. (Paris) .

Réponses corticales "secondaires" à la stimulation sensorielle chez le chat curarisé non anesthésié.

Popov, Mme C. (Paris).

Contribution à l'étude du mécanisme d'élaboration des connexions corticales dans le conditionnement d'après des expériences électrocorticographiques sur le lapin.

Dongier, S., Gastaut, Y. et Dongier, M. (Marseille).

Enregistrement polygraphique de l'effet de surprise. Relations entre les résultats obtenus et les données cliniques.

Gastaut, H. (Marseille).

Etat actuel des connaissances sur l'électroencéphalographie du conditionnement.

Kennard, M. A., Schwartzman, A. E. et Fister, W. P. (Vancouver).

Etude de la fréquence des rythmes cérébraux dérivés des régions motrices, frontale, pariétale et occipitale effectuée chez des malades d'hôpital psychiatrique et chez des sujets normaux.

Walter, W. G. et Shipton, J. (Bristol).

La présentation et l'identification des composantes des rythmes alpha.

Shipton, J. et Walter, W. G. (Bristol).

Les relations entre les activités alpha, les modes de pensée et les affinités sociales.

Bekkering, J. D., Kamp, A., de Lange, J., Storm van Leeuwen, W. et Werre, P. F. (Leiden).

Corrélations entre l'analyse des fréquences et quelques phénomènes psychologiques.

Das, N. N. (Calcutta) et Gastaut, H. (Marseille).

Variations de l'activité électrique du cerveau, du cœur et des muscles squelettiques au cours de la méditation et de l'extase Yogique.

Mundy-Castle, A. C. (Johannesburg).

L'électroencéphalogramme et sa relation avec le tempérament.

Rémond, A. et Lesèvre, N. (Paris).

Remarques sur l'activité cérébrale des sujets normaux. La typologie électroencéphalographique dans ses rapports avec certains caractères psychologiques.

Faure, J. (Bordeaux).

Activité électrique du cerveau, comportement, fonctions cortico-viscérales en relation avec l'état hormonal chez l'animal et chez l'homme.

Schneider, J. (Colmar).

Activités rapides de type particulier et troubles du comportement.

Confrontation entre les données de l'électroencéphalogramme et des examens psychologiques chez 522 sujets répartis en trois groupes différents.

Gastaut, H., Dongier, M. et Jest, C. (Marseille).

I — Matériel et méthodes utilisés pour recueillir les données électroencéphalographiques et psychologiques.

Gallais, P., Collomb, H., Miletto, G., Cardaire, G. et Blanc-Garin, J. (Marseille).

II — Confrontations des données de l'électroencéphalogramme et de l'examen psychologique chez 113 jeunes soldats.

Picard, P., Navarranne, P., Laboureur, P., Grousset, G. et Jest, C. (Toulon).

III — Confrontations des données de l'électroencéphalogramme et de l'examen psychologique chez 309 candidats pilotes à l'aéronautique.

Dongier, M., Dongier, S. et Angel-Villegas, G. (Marseille).

IV — Confrontations des données des examens psychologiques et de l'électroencéphalogramme chez 100 névrosés.

Lairy, G. C. et Dell, P. (Paris).

La régulation de l'activité corticale : Aspects psychophysiologiques et psychopathologiques.

Verdeaux, G. et J. et Frances, R. (Paris).

L'enregistrement polygraphique dans la perception visuelle et auditive.

Dreyfus-Brisac, C. et Fischgold, H. (Paris).

Veille, sommeil, réactivité sensorielle chez le prématuré, le nouveau-né et le nourrisson, introduction.

Dreyfus-Brisac, C., Samson-Dollfus, D. et Sainte-Anne-Dargassies, S. (Paris).

I — Veille, sommeil et réactivité sensorielle chez le prématuré.

Dreyfus-Brisac, C. et Monod, M. (Paris).

II — Veille, sommeil et réactivité chez le nouveau-né à terme.

Dreyfus-Brisac, C. et Blanc, C. (Paris).

III — Aspects électroencéphalographiques de la maturation cérébrale pendant la première année de la vie.

Réactivité, tracé EEG et modification de la conscience.

Fischgold, H., Arfel, G., Torubia, H. et Mathis, P. (Paris)

I — Variations du rythme respiratoire et du rythme cardiaque au cours des paroxysmes de P. O. bilatéraux synchrones.

Mathis, P., Torubia, H. et Fischgold, H.

II — Réactivité, périodicité et corrélation cortico-cardio-respiratoire dans le coma.

Kernen, R., Arfel, G. et Mathis, P.

Réactivité et absence de réactivité du tracé électroencéphalographique dans l'anesthésie.

Order for immediate delivery from

Masson et Cie, Publishers,
120 Blvd. St. Germain, Paris VI-e

or

THE EEG JOURNAL,
3801 University Street, Montreal

INDEX TO CURRENT LITERATURE

Edited by CHARLES E. HENRY

Institute of Living, Hartford, Conn. U.S.A.

AASS, F., KAADA, B. R. and TORP, K. H. The diagnostic and prognostic value of the initial EEG in children with convulsions. *Acta. Pediat.*, Stockholm, **1956**, *45*: 335-342.

ACKNER, B. and PAMPIGLIONE, G. Some relationships between peripheral vasomotor and EEG changes. *J. Neurol. Neurosurg. Psychiat.*, **1957**, *20*: 58-64.

AIRD, R. B., STRAIT, L. A., PAGE, J. W., HRENOFF, M. K. and BOWDITCH, S. C. Current pathway and neurophysiologic effects of electrically induced convulsions. *J. nerv. ment. Dis.*, **1956**, *123*: 505-512.

ALBE-FESSARD, E., BUSER, P. et ROUGEUL, A. Activités bilatérales tardives évoquées sur le cortex du chat sous chloralose par stimulation d'une voie somesthésique. *J. Physiol.*, Paris, **1955**, *47*: 69-72.

ALBERNAZ, J. G. e ALBERNAZ, D. S. Valor do sono natural ou induzido no eletrencefalograma. Resultado de 500 observações em pacientes com moléstia convulsiva. *Arq. neuro-psiquiat.*, S. Paulo, **1956**, *14*: 316-320.

ANDREANI, F. e PINELLI, P. Delta periodico in un caso con sindrome da trombosi dell'arteria cerebrale anteriore complicata da confusions mentale. *Riv. Neurol.*, **1955**, *25*: 589-597.

ANDRÉ-BALISAUX, G. et BRIHAYE, J. Agénésies et lipomes du corps calleux. *Schweiz. Arch. Neurol. Psychiat.*, **1956**, *77*: 367-380.

ANDY, O. J. and CHINN, R. McC. Cingulate gyrus seizures: Correlation of electroencephalographic and behavioral activity in the cat. *Neurol.*, **1957**, *7*: 56-68.

ARDITO, R. Rilievi elettroencefalografico e clinici in conque casi di epilessia fotogenica. *Riv. Neurol.*, **1955**, *25*: 655-659.

ARDITO, R. Su di case di automatismi di piccolo male. *Riv. Neurol.*, **1955**, *25*: 613-616.

BAIRD, III, H. W. and BOROFSKY, L. G. Infantile myoclonic seizures. *J. Pediat.*, **1957**, *50*: 332-339.

BAIRD, III, H. W., WYCIS, H. T. and SPIEGEL, E. A. Convulsions in tuberous sclerosis controlled by the elimination of impulses originating in the basal ganglia. *J. Pediat.*, **1956**, *49*: 165-172.

BALDWIN, M., FROST, L. L. and WOOD, C. D. Face and jaw movements during epileptiform discharge in temporal regions. *Neurol.*, **1957**, *7*: 15-25.

BECKETT, P. G. S., BICKFORD, R. G. and KEITH, H. M. The electroencephalogram in various aspects of mental deficiency. *Amer. J. Dis. Child.*, **1956**, *92*: 374-381.

BEHRMAN, S. and KNIGHT, G. Carotid sinus epilepsy and its treatment by denervation. *Brit. med. J.*, **1956**, No. 5008, 1522-1525.

BERNSTINE, R. L., BORKOWSKI, W. J. and PRICE, A. H. Prenatal fetal EEG. *Amer. J. Obstet. Gynaec.*, **1955**, *70*: 623-630.

BJERGLUND, R. and BRANDT, S. Electroencephalographic findings in children with febrile convulsions. *Ugeskr. Laeg.*, **1954**, *116*: 1423.

BLONSTEIN, J. L. and CLARKE, E. Further observations on the medical aspects of amateur boxing. *Brit. med. J.*, **1957**, No. 5015, 362-364.

BREMER, F., BRIHAYE, J. et ANDRÉ-BALISAUX, G. Physiologie et pathologie du corpus calleux. *Schweiz. Arch. Neurol. Psychiat.*, **1956**, *78*: 31-87.

BUREŠ, J. Some metabolic aspects of Leão's spreading depression. *J. Neurochem.*, **1956**, *1*: 153-158.

BUSER, P. et ROUGEUL, A. Réception intracellulaire au niveau des cellules pyramidales de la corne d'Ammon du chat. *J. Physiol.*, Paris, **1955**, *47*: 121-123.

CALVET, J., CATHALA, H. P., HIRSCH, J. et SCHERRER, J. La réponse corticale visuelle de l'homme étudiée par une méthode d'intégration. *C. R. Soc. Biol.*, Paris, **1956**, *150*: 13481-351.

CANALI, G. Studio elettroencefalografico sulla poliomielite; nota preliminare. *Minerva pediat.*, **1955**, *7*: 747-756.

CANAVESIO, D. Elettroencefalogrammi negli stati metapsichici. *Ann. neuropsichiat. psicanal.*, **1955**, *2*: 21-31.

CASADO DE FRIAS, E. and MINKOWSKI, A. Convulsions in the newborn. *Acta pediat. espań.*, **1955**, *13*: 389-412.

CASPERS, H. Förderung und Hemmung von Narkoticawirkungen auf das Zentralnervensystem durch elektrische Stammhirnreizungen mit verschieden Reizgrössen. *Z. ges. exp. Med.*, **1955**, *125*: 386-400.

CASTORINA, G. e VIZIOLI, R. Studio comparativo dell'esame angiografico ed elletroencefalografico e vantaggi della loro associazione in 120 casi di tumori cerebrali sopratentorali. *Boll. Accad. Med. Roma*, **1955**, *3*: 13.

CAVANAGH, J. B. and MEYER, A. Aetiological aspects of Ammon's horn sclerosis associated with temporal lobe epilepsy. *Brit. med. J.*, **1956**, No. 5006, 1403-1407.

CHUSID, J. G., KOPELOFF, L. M. and KOPELOFF, N. Epileptic effects of intracisternal alumina cream in monkeys. *J. Neurosurg.*, **1956**, *13*: 582-586.

CLEMENTE, C. D., SUTIN, J. and SILVERSTONE, J. T. Changes in electrical activity of the medulla on the intravenous injection of hypertonic solutions. *Amer. J. Physiol.*, **1957**, *188*: 193-198.

COHN, R. Laminar electrical responses in lateral geniculate body of cat. *J. Neurophysiol.*, **1956**, *19*: 317-324.

COMBS, C. M. Bulbar regions related to localized cerebellar afferent impulses. *J. Neurophysiol.*, **1956**, *19*: 285-300.

CORDIER, J., DUREUX, J. B. et BARBIER, J. L'électroencéphalogramme au cours des dégénérescences tapéto-rétiniennes. *Rev. otoneur.*, Paris, **1956**, *28*: 193-216.

CREUTZFELDT, O. Die Krampfausbreitung im Temporallappen der Katze. *Schweiz. Arch. Neurol. Psychiat.*, **1956**, *77*: 163-194.

CREUTZFELDT, O., BAUMGARTNER, G. und SCHOEN, L. Reaktionen einzelner Neurone des senso-motorischen Cortex nach elektrischen Reizen. *Arch. f. Psychiat. u. Z. Neurol.*, **1956**, *194*: 597-619.

CREUTZFELDT, O., KASAMATSU, A. und VAZ-FERREIRA, A. Aktivitätsänderungen einzelner corticaler Neurone im akuten Sauerstoffmangel und ihre Beziehungen zum EEG bei Katzen. *Pflüg. Arch.*, **1957**, *263*: 647-667.

CRITCHLEY, MACD. Medical aspects of boxing, particularly from a neurological standpoint. *Brit. med. J.*, **1957**, No. 5015, 357-362.

DAUMEZON, G. et LAIRY, G. C. Dynamique du rythme alpha en psychopathologie. *Ann. méd.-psychol.*, **1957**, *115*: 35-51.

DEJONG, R. N. "Psychomotor" or "temporal lobe" epilepsy: A review of the development of our present concepts. *Neurol.*, **1957**, *7*: 1-14.

DELGADO, J. M. R. and MIHAILOVIČ, L. Use of intracerebral electrodes to evaluate drugs that act on the central nervous system. *Ann. N. Y. Acad. Sci.*, **1956**, *64*: 644-666.

DOTY, R. W., RUTLEDGE, JR., L. T. and LARSEN, R. M. Conditioned reflexes established to electrical stimulation of cat cerebral cortex. *J. Neurophysiol.*, **1956**, *19*: 401-415.

DRUCKMAN, R. and CHAO, D. Laughter in epilepsy. *Neurol.*, **1957**, *7*: 26-36.

ECCLES, J. C. *The Physiology of Nerve Cells.* Baltimore, Johns Hopkins Press, **1957**, 270 pp.

FRITZSCHE, H. and FRITZSCHE, I. Electroencephalographic changes in oxycephalus. *Z. Kinderheilk.*, **1956**, *78*: 158-165.

FORTE, A. L'epilessia addominale (contributo clinico ed EEG). *Ann. neuropsichiat. psicanal.*, **1955**, *2*: 501-510.

FRANÇOIS, J., STEFENS, R. et DE ROUCK, A. L'électroencéphalographie dans la toxoplasmose congénitale. *Schweiz. Arch. Neurol. Psychiat.*, **1956**, *77*: 338-353.

FRENCH, J. D. and KING, E. E. Mechanisms involved in the anesthetic state. *Surgery*, **1955**, *38*: 228-238.

GARSCHE, R. The electroencephalogram in tuberculous meningitis in childhood after termination of treatment. *Z. Kinderheilk.*, **1955**, *75*: 613.

GAUTHIER, C., MOLLICA, A. and MORUZZI, G. Physiological evidence of localized cerebellar projections to bulbar reticular formation. *J. Neurophysiol.*, **1956**, *19*: 468-483.

GONSETTE, R. et MONTANINI, R. A propos d'une intoxication au plomb d'allure familiale (Aspects cliniques et électroencéphalographiques). *Acta neurol. psychiat. Belg.*, **1956**, *56*: 813-826.

GÖTZE, W. Uber die Auslösung von Krampfanfällen durch innere Erkrankungen. *Klin. med.*, **1955**, *10*: 46-61.

GOZZANO, M., RICCI, G., e VIZIOLI, R. Riposte rinencefaliche a stimoli olfattori. *Arch. fisiol.*, **1954**, *54*: 320-329.

GRAFSTEIN, B. Locus of propagation of spreading cortical depression. *J. Neurophysiol.*, **1956**, *19*: 308-316.

GROSSMAN, H. J., GIBBS, E. L. and SPIES, H. W. Electroencephalographic studies on children having measles with no clinical evidence of involvement of the central nervous system. *Pediatrics*, **1956**, *18*: 556-560.

GRÜSSER, O. J. und CREUTZFELDT, O. Eine neurophysiologische Grundlage des Brücke-Bartley-effekts: Maxima der Impulsfrequenz Retinaler und corticaler Neurone bei Flimmerlicht mittlerer Frequenzen. *Pflüg. Arch.*, **1957**, *263*: 668-681.

HAMUY, T. P., BROMILEY, R. B. and WOOLSEY, C. N. Somatic afferent areas I and II of dog's cerebral cortex. *J. Neurophysiol.*, **1956**, *19*: 485-499.

HENNEAUX, J. Malformations vertébrales et division palatine chez deux sœurs, associées, chez l'une d'elles, à une agénésie du corps calleux. *Schwiez. Arch. Neurol. Psychiat.*, **1956**, *77*: 433-441.

JANKE, M. Uber das auftreten Generalisierter Krampfpotentiale im EEG bei psychischer Anspannung, namentlich bei Diktatschreiben, Rechenaufgaben und technischen Manipulationen. *Nervenarzt*, **1956**, *27*: 393-402.

KRUMP, J. E. Die klinische Bedeutung des Hirnstrombildes (EEG) bei pernicioser Anämie. *Arch. klin. med.*, **1955**, *201*: 730-744.

KUGLER, J. und KREUZBAUER, F. EEG-befunde bei Glioblastomen. *Nervenarzt*, **1956**, *27*: 388-393.

LAIRY, G. C. Organisation de l'électroencéphalogramme normal et pathologique. *Rev. Neurol.*, Paris, **1956**, *94*: 749-801.

LAMBIASE, M. Azione dell'estere di (glucosi-I-monofosfato) sull'attività elettrica cerebrale. *Acta Neurol.*, Napoli, **1956**, *11*: 1195-1218.

LANDOLT, H. Uber die Symptomatologie der epileptischen Absenz mit spike-and-wave-Komplexen im EEG. *Schweiz. Arch. Neurol. Psychiat.*, **1956**, *78*: 377-383.

LANZONI, E. Electroencephalographic findings in infants during sleep induced by 3-methyl-1-pentyn-3-ol (Dormison). *Clin. Pediat.*, **1955**, *37*: 323-332.

LIBERSON, W. T. Electroencephalography. *Amer. J. Psychiat.*, **1957**, *113*: 601-604.

LONDON, N. J., RICHTER, P. and BLISS, E. L. Temporal lobe (psychomotor) epilepsy. *Psychosomat. Med.*, **1956**, *18*: 427-433.

MACCHI, G. e CARRERAS, M. Sull'importanza del segno della carotide in EEG. *Riv. Neurol.*, **1955**, *17*: 597-603.

MANCINI, G. e BRUNO, V. Influenca dei ritmi stagionali sull'accessualità epilettica. *Riv. Neurobiol.*, **1956**, *2*: 425-439.

MERLIS, S. and DENBER, H. C. B. Studies on Mescaline. V. Electroencephalographic evidence for the antagonism between mescaline and chlorpromazine hydrochloride. *J. nerv. ment. Dis.*, **1956**, *123*: 542-545.

MILLETTI, M. Neurosurgical aspects of epilepsy in children. *Clin. Pediat.*, **1955**, *37*: 3-60.

MONNIER, M. et BAMATTER, F. Le syndrome électroencéphalographique des embryopathies par toxoplasmose. *Schweiz. Arch. Neurol. Psychiat.*, **1956**, *77*: 250-266.

MURAMATSU, M. Influence of several kinds of anesthetic upon the brain wave of cats. *Folia Pharmacol. Japon.*, **1954**, *50*: 443.

NACHMANSOHN, D. and MERRITT, H. H. (Ed.) Nerve Impulse (Transactions of the Fifth Conference). New York: Josiah Macy, Jr. Foundation, **1956**, 256 p.

NORDIO, S. and PISTONE, F. Adenosintriphosphoric acid and encephalograms. *Clin. Pediat.*, **1955**, *37*: 199.

OCHS, S. The direct cortical response. *J. Neurophysiol.*, **1956**, *19*: 513-523.

OPITZ, O. and KREUZER, F. Behavior of rabbit brain (EEG observations) in ischemia and anoxia after adaptation for altitude. *Pflüg. Arch. ges. Physiol.*, **1955**, *260*: 480.

OSTOW, M. Psychic function of temporal lobe as inferred from seizure phenomena. *Arch. Neurol. Psychiat.*, Chicago, **1957**, *77*: 79-85.

PAMPIGLIONE, G. Some anatomical considerations upon electrode placement in routine EEG. *Proc. E.P.T.A.*, **1956**, *7*: 1-11.

PAMPUS, F. und GROTE, W. Elektrencephalographische und klinische Befunde bei Boxern und ihre Bedeutung für die Pathophysiologie der traumatischen Hirnschädigung. *Arch. Psychiat. Zeit. Neurol.*, **1956**, *194*: 152-178.

PARIANTE, F., SERRA, C. e LAMBIASE, M. Correlazioni biologiche e clinico-elettroencefalografiche nelle sindromi nevrotiche. *Acta Neurol.*, Napoli, **1957**, *11*: 1-79.

PARDELLI, L. and ARDITO, R. The electroencephalogram in febrile convulsions in childhood. *Riv. clin. pediat.*, **1954**, *53*: 233.

PERRIS, C. e STANCATI, G. Reperti elettroencefalografici nelle sindromi psichiatriche. *Rass. Neuropsich.*, **1955**, *9*: 266-331.

PETERS, J. J., VONDERAHE, A. R. and POWERS, T. H. The functional chronology in developing chick nervous system. *J. Exp. Zool.*, **1956**, *113*: 505-518.

PETSCHE, H. und MARKO, A. Das Photozellentoposkop, eine einfache Methode zur Bestimmung der Feldverteilung und Ausbreitung hirnelektrischer Vorgänge. *Arch. Psychiat. Zeit. Neurol.*, **1954**, *192*: 447-462.

PIEKENBROCK, T. C., TAYLOR, R. C. and BECKA, D. R. EEG during electroconvulsive therapy with succinylcholine. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *76*: 653-659.

PURPURA, D. P. and GRUNDFEST, H. Nature of dendritic potentials and synaptic mechanisms in cerebral cortex of cat. *J. Neurophysiol.*, **1956**, *19*: 573-595.

RIVOLTA, A. e CARRERAS, M. Crisi psicomotorie e focus e.e.g. temporale nel corso di una ipoglicemia spontanea da adenoma insulare del pancreas. *Riv. Neurobiol.*, **1956**, *2*: 467-478.

RIVOLTA, A. e MIGLIORE, A. L'esame elettroencefalografico nella diagnosi delle affezioni vascolari cerebrali e meningee. *Riv. Neurol.*, **1955**, *25*: 373-400.

ROBERTS, A. C. A psychometric concomitant of bioccipital spike seizure foci. *Dis. nerv. Syst.*, **1957**, *18*: 7-11.

RUOSI, D. Stato di male epilettico postraumatico e pneumoencefalografia. *Ann. neuropsichiat. psicanal.*, **1955**, *2*: 563-570.

RUOSI, D. e RICCIO, R. Sulla disostosi cleidocranica. Contributo clinico, radiologico, elettroencefalografico. *Ann. neuropsichiat. psicanal.*, **1956**, *3*: 458-480.

SARROUY, CH., SAINT-JEAN, Mme and SENDRA, L. Prognosis of tuberculous meningitis by electroencephalogram. *Pédiat.*, Lyon, **1955**, *43*: 697-702.

SARTESCHI, P. e ARDITO, R. Reperti clinici ed EEG in 100 casi di epilessia dell'età tardiva ed involutiva. *Riv. Neurobiol.*, **1956**, *2*: 415-424.

SARTESCHI, P. e ARDITO, R. Segnalazione di uno "stato di male elettrico" in un casso di neurolue. *Riv. Neurobiol.*, **1956**, *2*: 405-413.

SAUGUET, H. et DELAVELEYE, R. Rôle des facteurs psychiques dans les convulsions infantiles et les paroxysmes épileptiques au cours de l'enfance et de l'adolescence. *Ann. méd.-psychol.*, **1956**, *114*: 760-827.

SEGUNDO, J. P. and MACHNE, X. Unitary responses to afferent volleys in lenticular nucleus and claustrum. *J. Neurophysiol.*, **1956**, *19*: 325-339.

SERRA, C. e KEMALIN, D. Ricerche elettroencefalografiche in un caso di amaurosi isterica. *Boll. Soc. Ital. Biol. sper.*, **1956**, *32*: 636-639.

SERRA, C. e MASTROGIOVANNI, P. D. Studio dell'attività elettrica corticale sotto carico di acido adenosintrifosforico. *Acta Neurol.*, Napoli, **1956**, *11*: 912-934.

SHAGASS, C. Sedation threshold: A neurophysiological tool for psychosomatic research. *Psychosomat. Med.*, **1956**, *18*: 410-419.

SHARPLESS, S. and JASPER, H. Habituation of the arousal reaction. *Brain*, **1956**, *79*: 655-680.

SKATVEDT, M. and LUNDERVOLD, A. The significance of electrographic spike foci in patients with cerebral palsey without epileptic seizures. *Acta. Pediat.*, Stockholm, **1956**, *45*: 440-443.

SUTIN, J. and CLEMENTE, C. D. Localized response in the posterior hypothalamus following intravenous administration of pitressin. *Amer. J. Physiol.*, **1957**, *188*: 199-204.

SVORAD, D. Reticular activating system of brain stem and "animal hypnosis." *Science*, **1957**, *125*: 156.

TERZIAN, H. e CECOTTO, C. Occlusione sperimentale della carotide commune e della cerebrale media: modificazioni elettroencefalografiche determinate della variazioni pressorie. *Riv. Neurol.*, **1955**, *25*: 536-543.

TERZIAN, H. e RUBERTI, R. Studio sperimentale dell'azione del largactil e del pendiomid sul l'attivita elettrica cerebrale del coniglio. *Riv. Neurol.*, **1954**, *24*: 686-701.

TURNER, M. and BERARD, E. Effect of chlorpromazine on the (human) electroencephalogram and electrodermogram. *Rev. Soc. argent. de biol.*, **1954**, *30*: 163.

TURRELL, R. C., LEVY, L. L. and ROSEMAN, E. The value of the electroencephalogram in selected cases of subdural hematoma. *J. Neurosurg.*, **1956**, *13*: 449-454.

VENTRA, D. et SERRA, C. 5-idrossitriptamina, sistema nervoso vegetativo e attività elettrica cerebrale. *Acta Neurol.*, Napoli, **1956**, *11*: 935-958.

VERHAEGEN, P. L'electroencephalogramme de l'autochtone congolais et les différences raciales. *Acta neurol. psychiat. Belg.*, **1956**, *56*: 842-852.

VIZIOLI, R. e MARCHINI, E. Inibizione di spikes temporali con stimolazione luminosa intermittente. *Riv. Neurol.*, **1955**, *25*: 631-636.

ELECTROENCEPHALOGRAPHY
AND
CLINICAL NEUROPHYSIOLOGY

AN INTERNATIONAL JOURNAL

Published by

THE INTERNATIONAL FEDERATION OF SOCIETIES
FOR ELECTROENCEPHALOGRAPHY AND CLINICAL
NEUROPHYSIOLOGY, Inc.

PARIS, 1949

Chief Editorial Office, 3801 UNIVERSITY ST. MONTREAL, CANADA

JOURNAL SUPPLEMENTS

1. *Bibliography of Electroencephalography,* 1875-1948,

   by MARY A. B. BRAZIER,
   Montreal, 1950, 178 pages, price $3.25.

2. *Second International Congress Symposia,*

   edited by H. FISCHGOLD, Paris, 1949, 137 pages (out of print).

3. *Third International Congress — Communications,*

   edited by R. SCHWAB, J. MERLIS, E. WALKER and
   C. HENRY, Cambridge, 1953. 94 pages, price $2.00.

4. *Third International Congress — Symposia,*

   edited by E. WALKER, J. MERLIS and C. HENRY,
   Cambridge, 1953, 260 pages, price $5.00.

5. *Encéphalites et Encéphalopathies,*

   by J. RADERMECKER,
   Masson & Cie, Paris, 1956, 243 pages, price $8.00.

6. *Conditionnement et Réactivité en Electroencéphalographie*

   (Colloque de Marseille, 1955)

   edited by H. FISCHGOLD and H. GASTAUT,
   Masson & Cie, Paris, 1957, 475 pages, price $15.00.

Order from

THE EEG JOURNAL

3801 University Street - - Montreal 2, Canada